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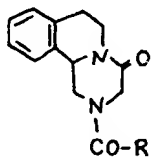
(54) PYRAZINO-ISOQUINOLINE DERIVATIVES

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG, of 250, Frankfurter Strasse, 61 Darmstadt, Federal Republic of Germany, a Joint-Stock Company organised under the laws of the Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new 2 - acyl - 4 - oxo - hexahydro - 4H-pyrazino[2,1 - a]isoquinoline derivatives and with the preparation thereof.

The new isoquinoline derivatives according to the present invention are compounds of the general formula:—



(I)

wherein COR is an acyl radical containing up to 26 carbon atoms derived from an unsubstituted or substituted aliphatic, cycloaliphatic, cycloalkylaliphatic, arylaliphatic or heterocyclic carboxylic acid or a substituted aromatic carboxylic acid by removal of the hydroxyl group from the carboxylic radical; and the physiologically compatible salts and quaternary ammonium salts thereof.

For sake of brevity, in the following description, the abbreviation "HPI" is used for 4-oxo - 1,2,3,6,7,11b - hexahydro - 4H - pyrazino[2,1 - a]isoquinoline and "—HPI" is used for - 4 - oxo - 1,2,3,6,7,11b - hexahydro-4H - pyrazino[2,1 - a]isoquinoline. Consequently, the compounds of general formula (I) can be referred to as "2-acyl-HPI".

We have found that the compounds of general formula (I) have a good compatibility and possess outstanding pharmacological properties. They are, *inter alia*, effective as anthelmintics and have an especially wide spectrum of activity against cestodes and trematodes. Furthermore, some of the new compounds have psychotropic and blood pressure-influencing properties. Therefore, the new compounds of general formula (I) can be used as pharmaceuticals in human and/or

veterinary medicine, especially as anthelmintics. Furthermore, they are useful as intermediates for the preparation of other pharmaceuticals.

Not only the racemic compounds of general formula (I) but als their optical antipodes are effective, especially those which, with regard to the optical configuration, correspond to the laevorotary HPI.

Amongst the 2-acyl-HPI of general formula (I) there are preferred the following compounds of general formulae (Ia) to (Ik), which correspond to general formula (I) and wherein the acyl radical (—CO—R) has the following meanings:

Ia a benzoyl group which is substituted once in the *o*-position by fluorine or in the *m*- or *p*-position by fluorine, chlorine, nitro, hydroxy, amino, formylamino, acetylamino, pentanoylamino, hexanoylamino, octanoylamino, oleoylamino, methoxyacetylamino, methylamino, dimethylamino or allylamino;

Ib a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptylcarbonyl group, each of which can be additionally substituted once by fluorine, chlorine, nitro, hydroxy, amino, formylamino, acetylamino, pentanoylamino, hexanoylamino, octanoylamino, oleoylamino, methoxyacetylamino, methylamino, dimethylamino or allylamino;

Ic an alkanoyl group with up to 8 carbon atoms, which can be additionally substituted by methoxy or ethoxy;

Id furyl - 2 - carbonyl, furyl - 3 - carbonyl, thienyl - 2 - carbonyl, thienyl - 3-carbonyl or 2 - thienylmercaptomethylcarbonyl;

Ie a 2-, 3- or 4-pyridyl-carbonyl or 2-, 3- or 4 - N - oxidopyridyl - carbonyl group which can be additionally substituted once by fluorine, chlorine, hydroxy, amino, formylamino, acetylamino, pentanoylamino, hexanoylamino, octanoylamino, oleoylamino, methoxyacetylamino, methylamino or dimethylamino;

If an aminoalkanoyl- (with up to 4 carbon atoms), amino - cycloalkyl - carbonyl (with 6 to 8 carbon atoms), aminobenzoyl- or aminopyridyl-carbonyl group, which is substituted on the nitrogen atom by benzylidene, 2 - hydroxybenzylidene, 2 - hydroxy - 3 - methoxy - benzylidene, carboxymethylidene, 3 - phenyl - prop-2 - enylidene or furfurylidene;

Ig a phenylazobenzoyl group, the terminal phenyl radical of which is substituted in the *p*-position by hydroxy, alkoxy with up to 4 carbon atoms amino alkylamino with up to 4 carbon atoms or dialkylamino with up to 8 carbon atoms and at the other positions can be additionally substituted by carboxy, aliphatic acylamino with up to 4 carbon atoms, halogen, sulpho or alkyl with up to 4 carbon atoms;

Ih an amino - cycloalkyl - carbonyl group with 6—8 carbon atoms, an aminobenzoyl group or an aminopyridylcarbonyl group, the amino groups of which are protected by a benzyl group which can be substituted by hydroxy and/or methoxy;

Ii a thiazolyl-, isothiazolyl-, oxazolyl- or isoxazolyl-carbonyl group which can be additionally substituted by methyl or nitro;

Ik a 2-, 3- or 4-piperidyl-carbonyl group which is substituted on the nitrogen atom by formyl, acetyl, pentanoyl, hexanoyl, octanoyl, oleoyl, methoxyacetyl, carboxymethyl, allyl, benzyl (which can be additionally substituted by hydroxy or methoxy) or 3-phenylpropyl;

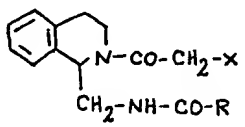
as well as the physiologically compatible salts, quaternary ammonium salts and optical antipodes of the compounds Ia to Ik.

In particular, compounds of general formula (I) are preferred in which the radical R has the following meaning: cyclohexyl, *o*-, *m*- and *p*-fluorophenyl, *p*-chlorophenyl, *m*- and *p*-aminophenyl, *m*- and *p*-formylaminophenyl, *p*-nitrophenyl and 3-pyridyl, as well as methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cycloheptyl, *m*-chlorophenyl, *m*- and *p*-hydroxyphenyl, *m*- and *p*-methylaminophenyl, *m*- and *p*-dimethylaminophenyl, *m*- and *p*-acetylaminophenyl, *m*- and *p*-methoxyacetylaminophenyl, 2-thienyl, 3-thienyl, thienyl-2-mercaptomethyl, 2-furyl, 2- and 3-pyridyl and 1-oxido-3-pyridinio.

The compounds of general formula (I) can be prepared by reacting 4 - oxo - 1,2,3,6,7,11b-hexahydro - 4H - pyrazino[2,1-a]isoquinoline (HPI) with a compound of the general formula:—

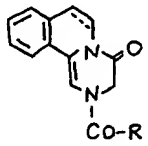
R—COOH (II)

wherein R has the same meaning as above, or with a functional derivative thereof; or by cyclising a compound of the general formula:—



(III)

wherein R has the same meaning as above and X is fluorine, chlorine, bromine, iodine, methylsulphonyloxy or arylsulphonyloxy with 6 to 10 carbon atoms, preferably *p*-toluenesulphonyloxy, in the presence of a cyclising agent under conditions splitting off HX; or by treating a compound of the general formula:—



(IV)

wherein R has the same meaning as above and the broken line means that a double bond can be present in the 6,7-position of the ring system, with a reducing agent; whereafter, if desired, the radical R in a compound obtained is converted, in a manner known from and described in the literature, into a different radical R and/or a racemic compound (I) obtained is resolved into its optical antipodes and/or a base of the general formula (I) is converted into its physiologically compatible acid addition salts or quaternary ammonium salts or a base of general formula (I) is liberated from its acid addition salts.

Generally speaking, the radical R can stand, for example, for one of the following radicals: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl or a heterocyclic radical.

The alkyl radical can be straight-chained or branched and contain up to 17 and especially up to 6 carbon atoms. The cycloalkyl radical can contain 3—12 and preferably 3—7 carbon atoms and 2 or 3 carbon atoms can also be joined together by endoalkylene bridges. The cycloalkyl radical can, in particular, contain up to 8 carbon atoms and the aralkyl radical preferably up to 10 carbon atoms. The aryl radical can be partially or, in the case of the naphthyl radical, also fully hydrogenated and can contain up to 10 carbon atoms. Finally, the heterocyclic radical can contain up to 15 carbon atoms and possibly be connected by a straight or branched alkyl or thiaalkyl group (containing up to 4 carbon atoms) with the adjacent carbonyl group. Additional double and/or triple bonds can also be present in the alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and heterocyclic radicals; furthermore, these radicals can also be substituted.

R preferably has one of the following meanings:

an alkyl radical containing up to 8 carbon atoms, which can be substituted by alkoxy containing up to 4 carbon atoms; a cycloalkyl radical containing up to 7 carbon atoms, which can be substituted by fluorine, chlorine, nitro, amino, alkylamino or dialkylamino, each containing up to 4 carbon atoms in the alkyl radical, allylamino, benzylamino (which can also be substituted by hydroxy and/or methoxy), saturated and unsaturated aliphatic acylamino containing up to 18 carbon atoms, amino protected as Schiff's base, hydroxy or alkoxy containing up to 4 carbon atoms;

a phenyl radical which is substituted by fluorine, chlorine, nitro, amino, alkylamino or dialkylamino, each containing up to 4 carbon atoms in the alkyl radical, allylamino, benzylamino (which can be substituted also by hydroxy and/or methoxy), saturated or unsaturated aliphatic acylamino containing up to 18 carbon atoms, amino protected as Schiff's base, hydroxy or alkoxy containing up to 4 carbon atoms, phenylazo (which can also be substituted by hydroxy, methoxy, amino, methylamino, dimethylamino, fluorine, chlorine or lower alkyl), carboxymethylamino or alkoxyacetylamino containing up to 4 carbon atoms in the alkoxy radical;

a thienyl, thienylmercaptomethyl, furyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl or pyridyl radical;

or a piperidyl radical which can be substituted by alkyl containing up to 4 carbon atoms, benzyl or saturated or unsaturated aliphatic acyl containing up to 18 carbon atoms.

In the following, the radicals R are defined in more detail:

alkyl preferably contains up to 6 carbon atoms and can be, for example, one of the following radicals: methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, *n*-pentyl, 1 - methyl - *n* - butyl, 2 - methyl - *n* - butyl, isopentyl, 1 - ethyl - propyl, 1,1 - dimethyl-*n* - propyl, *tert.* - pentyl, *n*-hexyl, 1,1 - dimethyl - *n* - butyl, 2,2 - dimethyl - *n* - butyl, isohexyl, *n*-heptyl, 1,1 - dimethyl - *n* - pentyl, *n*-octyl or 2-ethylhexyl; but can also be, for example, *n* - nonyl, 1 - (*n* - butyl) - *n*-pentyl, *n*-decyl, *n*-undecyl, *n*-dodecyl, *n*-tridecyl, *n*-tetradecyl, *n*-pentadecyl, *n*-hexadecyl, *n*-heptadecyl, or other isomers of these radicals, for example, isodecyl, isododecyl or the like;

cycloalkyl can contain 3—12 and preferably 3—7 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl or cyclododecyl; 2 or 3 carbon atoms in the cycloalkyl radical can also be joined together by endoalkyl bridges, for example, by endoalkylene bridges containing up to 8 and preferably 1 or 2 carbon atoms, for example by $-CH_2-$, $-CH_2-CH_2-$,

$-C(CH_3)_2-$, $-CH_2CH_2CH_2-CH_2-$,

$-C(C_2H_5)_2-$ or

$-CH(CH_3)-CH(CH_3)-$;

examples of such bridged cycloalkyl radicals include bicyclo[2,2,1]heptyl-2, bicyclo[2,2,2]-octyl-2-, bicyclo[3,2,2]nonyl-2, -3 and -6, bicyclo[4,2,2]decyl-2, -3 and -7, bicyclo-[4,3,2]undecyl-2, -3, -7, -8 and -10 or adamantyl, as well as alkylated bicyclic systems, for example, 7 - methyl - bicyclo-[2,2,1]heptyl, 7 - ethyl - bicyclo[2,2,1]heptyl, 7,7 - dimethyl - bicyclo[2,2,1]heptyl, 7,7-diethylbicyclo[2,2,1]heptyl, 1,7,7 - trimethyl-bicyclo[2,2,1]heptyl, 1 - methyl - bicyclo-

[2,2,2]octyl and 1,2,3 - trimethyl - bicyclo-[2,2,2]octyl;

the cycloalkylalkyl radicals preferably contain up to 8 carbon atoms and can be, for example, cyclobutylmethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl or cyclohexylethyl.

The alkyl and cycloalkyl radicals can also contain unsaturated bonds, the following being examples thereof: ethenyl, ethynyl, 1-propenyl, 2-propenyl, 8-heptadecenyl, 1-cyclopentenyl, 2 - cyclopentenyl, 3 - cyclopentenyl, 1 - cyclohexenyl, 2 - cyclohexenyl, 3 - cyclohexenyl, 1-cycloheptenyl, 2 - cycloheptenyl, 3 - cycloheptenyl, 4 - cycloheptenyl, 1 - butenyl, 2-butenyl, 3 - butenyl, 1 - cyclooctenyl, 2-cyclooctenyl, 3 - cyclooctenyl, 4 - cyclooctenyl, 5-cyclooctenyl, 1-propynyl and 2-propynyl.

Aralkyl preferably contains up to 10 carbon atoms and can be, for example, benzyl, 1- or 2-phenylethyl, 3-phenylpropyl, 1-methyl-1-phenylethyl or 1-methyl-2-phenylethyl.

Aryl preferably contains up to 10 carbon atoms and can be, for example, substituted phenyl, naphthyl-1, naphthyl-2 or phenanthryl-1 (or -2, -3, -4, -9).

Naphthyl groups can also be partially or fully hydrogenated and can be, for example, 1,2 - dihydronaphthyl, 1,2,3,4 - tetrahydronaphthyl or decalinyl (*cis* or *trans*).

Heterocyclic radicals can be, for example, heteroaromatic five- and six-membered systems which can be condensed with one or two benzo groups or with a second five- or six-membered heterocycle, and are preferably, for example, pyrryl-1 (or -2 or -3), thienyl-2 (or -3), furyl-2 (or -3), indolyl-1 (or -2, -3, -4, -5, -6 or -7), benzofuryl-2 (or -3, -4, -5, -6 or -7), benzothienyl-2 (or -3, -4, -5, -6 or -7), pyridyl-2 (or -3 or -4), α- or γ-pyranyl-2 (or -3 or -4), α- or γ-thiopyranyl-2 (or -3 or -4), quinolyl-2 (or -3, -4, -5, -6, -7 or -8), isoquinolyl-1 (or -3, -4, -5, -6, -7 or -8), carbazolyl-1 (or -2, -3, -4 or -9), pyrazolyl-1 (or -3, -4 or -5), imidazolyl-1 (or -2, -4 or -5), benzpyrazolyl-1 (or -2, -4, -5, -6 or -7), benzimidazolyl-1 (or -2, -4 or -5), oxoazolyl-2 (or -4 or -5), benzoxazolyl-2 (or -4, -5, -6 or -7), thiazolyl-2 (or -4 or -5), benzthiazolyl-2 (or -4, -5, -6 or -7), isoxazolyl-3 (or -4 or -5), isothiazolyl-3 (or -4 or -5), 1,2,3-triazolyl-1 (or -2 or -4), 1,2,4-triazolyl-1 (or -3 or -5), tetrazolyl-1 (or -2 or -5), 1,2,3- or 1,2,4-oxadiazolyl, 1,2,4-, 1,3,4- or 2,1,5-thiadiazolyl, 2,1,3 - benzo - thiadiazolyl - 5, acridinyl-1 (or -2, -3, -4, -5, -6, -7, -8 or -9), pyridazinyl-3 (or -4), pyrimidinyl-2 (or -4 or -5), pyrazinyl, phenazinyl-1 (or -2), phenoxazinyl-1 (or -2, -3, -4 or -9), phenothiazinyl-1 (or -2, -3, -4 or -9), thianthrenyl-1 (or -2), 1,2,5-, 1,2,4- or 1,2,3-triazinyl, 1,2,3,4- or 1,2,4,5-tetrazinyl, purinyl-2 (or -6, -7, -8 or -9), pyrazolo[3,4-d]pyrimidinyl-2 (or -6, -7 or -9), pteridinyl, cinnolinyl-3 (or -4, -5, -6, -7 or -8), phthalazinyl-1 (or -5 or -6), quinazolinyl-2 (or -4, -5, -6, -7 or -8), quinoxalinyl-2 (or -5 or -6), 1,5-naphthyridinyl-2 (or -3 or -4) or nalidixinyl. The heterocyclic radicals can also be partially or fully hydrogenated and are preferably, for example, 1,4-dioxanyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrazolidinyl, imidazolidinyl, 1,2,3,4 - tetrahydropyridyl, 1,2,5,6 - tetrahydropyridyl, piperidyl, tetrahydropyranyl, 1,2,3,4 - tetrahydroquinolyl, 1,2,3,4 - tetrahydroisoquinolyl, hexahydropyridazinyl, hexahydropyrimidinyl, piperazinyl, 1,3-dioxanyl, pyrrolinyl, dihydrofuryl, pyrazolinyl, imidazolinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, 2,3-dihydrobenzthiazolyl, dihydropyridyl, dihydropyranyl, tetrahydrothiopyranyl, 1,2-dihydroquinolyl, 3,4-dihydroquinolyl, 1,2-dihydroisoquinolyl, 3,4-dihydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, chromenyl, chromanyl, dihydropyridazinyl, tetrahydropyridazinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, dihydropyrazinyl, tetrahydropyrazinyl or 1,4-thiazinyl.

These alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl or heterocyclic radicals can also be substituted one or more times, whereby several substituents can also be present on one carbon atom or the substituents, when possible, can be in cis- or trans relationship. Such substituents include, for example, one or more of the following:

alkyl containing up to 4 carbon atoms and preferably, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl and *tert.*-butyl; haloalkyl containing up to 4 carbon atoms, for example, fluoromethyl, trifluoromethyl and chloromethyl; hydroxyalkyl containing up to 4 carbon atoms, for example, hydroxymethyl and hydroxyethyl; aminoalkyl containing up to 4 carbon atoms, as well as the corresponding mono- and dimethyl-, as well as mono- and diethylamino radicals and preferably, for example, aminomethyl, methylaminomethyl, dimethylaminomethyl, methylaminoethyl, dimethylaminoethyl, ethylaminomethyl, diethylaminomethyl, ethylaminoethyl, diethylaminoethyl, methylamino-*n*-propyl, dimethylamino-*n*-propyl and diethylamino-*n*-butyl, etc.; aryl containing 6—10 carbon atoms and preferably, for example, phenyl; aralkyl containing 7 to 19 carbon atoms and preferably, for example, benzyl and triphenylmethyl; halogen, preferably fluorine or chlorine but also bromine or iodine; hydroxy; alkoxy containing up to 4 carbon atoms and preferably, for example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec.*-butoxy and *tert.*-butoxy; acyloxy containing up to 4 carbon atoms, for example formyloxy, acetoxy and propionyloxy; substituted acetoxy, for example, trifluoroacetoxy and methoxyacetoxy; aryloxy containing 6—10 carbon atoms, preferably phenoxy; sub-

stituted aryloxy, for example *o*-, *m*- and *p*-fluorophenoxy, *o*-, *m* and *p*-chlorophenoxy, *o*, *m* and *p*-aminophenoxy, *o*, *m* and *p*-methylaminophenoxy, *o*- *m*- and *p*-dimethylaminophenoxy, *o*-, *m*- and *p*-formylaminophenoxy and *o*, *m* and *p*-acetylaminophenoxy; amino, alkylamino containing up to 4 carbon atoms and preferably, for example, methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, isobutylamino, *sec.*-butylamino and *tert.*-butylamino; dialkylamino, each of the alkyl radicals of which contain up to 4 carbon atoms and preferably, for example, dimethylamino, diethylamino, methylethylamino, methyl - *n* - propylamino, methyl - isopropylamino, methyl - *n* - butylamino, ethyl - *n*-propylamino, ethyl - isopropylamino, ethyl - *n*-butylamino, di - *n* - propylamino, diisopropylamino and di - *n* - butylamino; trialkyl ammonium, each of the alkyl radicals of which contain up to 4 carbon atoms, for example, trimethylammonium and triethylammonium; alkenylamino containing up to 4 carbon atoms, for example, vinylamino, 1-propenylamino, allylamino, 1-butenylamino, 2-butenylamino and 3-butenylamino; aralkyl optionally substituted by hydroxyl, methoxy, methylamino, dimethylamino, methylthio, methyl and/or ethyl, for example, benzylamino, 2-hydroxybenzylamino and 2 - hydroxy - 3 - methoxybenzylamino; acylamino containing up to 18 carbon atoms, the acyl group of which is derived from a saturated or unsaturated fatty acid and preferably from a fatty acid containing up to 18 carbon atoms, for example, formylamino, acetylamino, propionylamino, butyrylamino, pentanoylamino, hexanoylamino, heptanoylamino, octanoylamino, decanoylamino, dodecanoylamino, palmitoylamino, stearoylamino, oleolylamino, linoloylamino and linolenoylamino; acylamino, the acyl group of which is derived from trifluoroacetic acid or from a lower alkoxyacetic acid (alkoxy containing up to 4 carbon atoms), for example, trifluoroacetylamino, methoxyacetylamino, ethoxyacetylamino, propoxyacetylamino, isopropoxyacetylamino, butoxyacetylamino and *tert.*-butoxyacetylamino; acylamino, the acyl group of which is derived from a dicarboxylic acid (containing 4 to 8 carbon atoms) which can form a cyclic anhydride, for example, 3-carboxypropionylamino (succinoylamino), 3-carboxy - *cis* - prop - 2 - enoylamino (maleinoylamino), 2 - carboxy - cyclopentylcarbonylamino, 2 - carboxy - cyclohexyl - carbonylamino, phthaloylamino, 2- and 3-carboxypyridyl - 3 - and - 2 - carbonylamino and 3-(carboxyethyl - mercapto) - propionoylamino; sulphamino; oxycarbonylamino substituted with an organic radical containing up to 15 carbon atoms, for example, ethoxycarbonylamino, *tert.* - butoxycarbonylamino, benzyloxycarbonylamino, 3,5 - dimethoxybenzyloxycarbonylamino, cyano - *tert.* - butoxycarbonylamino, 2 - biphenylyl - (4) - isopropoxycarbonylamino, 2,2,2 - trichloroethoxycarbonylamino, fluorenyl - (9) - methoxycarbonylamino, *p* - nitrobenzyloxycarbonylamino, *p* - chlorobenzyloxycarbonylamino, *p*-phenylazobenzyloxycarbonylamino, *p* - (*p*-methoxyphenylazo) - benzyloxycarbonylamino and cyclopentyloxycarbonylamino; alkylideneand aralkylideneamino containing up to 9 carbon atoms, for example, benzylideneamino, *p*-methylbenzylideneamino, *o*-hydroxybenzylideneamino, *p* - methoxybenzylideneamino, 3,4 - dimethoxybenzylideneamino, 2 - hydroxy-3 - methoxybenzylideneamino, isopropylideneamino, *sec.* - butylideneamino, carboxymethyleneamino, 3 - phenyl - 2 - propen - 1-ylideneamino, furfurylideneamino and 5-nitrofurfurylideneamino; sulpho and disulpho radicals resulting from bisulphite addition on the last-mentioned radicals, for example, α-sulpho - benzylamino, α - sulpho - 2-hydroxybenzylamino, α - sulpho - 2 - hydroxy-3 - methoxybenzylamino, sulphomethylamino, 1 - sulphoethylamino, 1 - sulpho - 1 - carboxymethylamino and (1,3 - disulpho - 3-phenyl)propylamino; phenylazo substituted (preferably *p*-substituted) by hydroxy, alkoxy containing up to 4 carbon atoms, for example, methoxy and ethoxy, amino, alkylamino containing up to 4 carbon atoms, for example, methylamino and ethylamino, and/or dialkylamino containing up to 8 carbon atoms, for example, dimethylamino and diethylamino, or naphthylazo-1 or -2, which can also be substituted by carboxy, lower alkoxycarbonyl, for example, methoxycarbonyl and ethoxycarbonyl, acylamino containing up to 4 carbon atoms, for example, formylamino and acetylamino, halogen, for example fluorine, chlorine and bromine, sulpho, alkoxysulphonyl, for example, methoxysulphonyl and ethoxysulphonyl, and/or alkyl containing up to 4 carbon atoms, for example, methyl, ethyl, propyl, isobutyl and *tert.*-butyl; thus, for example, 3 - carboxy-4 - hydroxyphenylazino, 4 - dimethylaminophenylazo, 4 - diethylaminophenylazo, 2-methyl - 4 - hydroxy - phenylazo, 4 - methoxy- and 4 - ethoxy - phenylazo; an amino group protected by a mono- or disaccharide radical containing 5 to 12 carbon atoms, preferably by a monosaccharide radical oxidised on carbon atom 1 and/or on the terminal carbon atom to the corresponding carboxylic acid, preferably, for example gluconoylamino, glucuronoylamino, saccharoylamino, galactonoylamino, galacturonoylamino, mucoylamino, mannonoylamino, manno - saccharoylamino, arabinonoylamino, ribonoylamino, maltobionoylamino, lactobionoylamino and saccharobionoylamino; mercapto; alkylmercapto containing up to 4 carbon atoms and preferably, for example, methylmercapto, ethylmercapto, *n*-propylmercapto, isopropylmercapto, *n*-butylmercapto, isobutylmercapto, *sec.*-butylmercapto and *tert.*-butylmercapto; aryl-

mercapto containing 6—10 carbon atoms, preferably phenylmercapto; acylmercapto containing up to 4 carbon atoms, for example, formylmercapto, acetylmercapto and propionylmercapto; thienyl-2-mercapto; thienyl-3-mercapto; nitro; cyano; carboxy; alkoxycarbonyl containing up to 4 carbon atoms in the alcohol component and preferably, for example, methoxycarbonyl, ethoxycarbonyl, *n* - propoxycarbonyl, isopropoxycarbonyl, *n* - butoxycarbonyl, isobutoxycarbonyl, *sec.* - butoxycarbonyl and *tert.*-butoxycarbonyl; hydrazino; alkyl- and arylhydrazino, for example, 1-methylhydrazino, 2-methylhydrazino, 1-ethylhydrazino, 2-ethylhydrazino, 1,2-dimethylhydrazino, 2,2 - dimethyl - hydrazino, 1,2,2 - trimethylhydrazino and 2 - phenylhydrazino; azido; sulpho; alkoxysulphonyl and aryloxysulphonyl containing up to 7 carbon atoms, for example, methoxysulphonyl, ethoxysulphonyl and *p*-tolueneoxysulphonyl; sulphur (as a thiono group) and/or oxygen, preferably as a keto or N-oxido group (N-oxide).

If secondary amino groups are present in the radical R, then these can be substituted by various acyl radicals, for example, by a saturated or unsaturated aliphatic acyl radical containing up to 18 carbon atoms, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, dodecanoyl, palmitoyl, stearoyl, oleoyl, linoloyl or linolenoyl; or by an alkoxyacetyl radical containing up to 4 carbon atoms in the alkoxy radical, for example, methoxyacetyl, ethoxyacetyl, propoxyacetyl, butoxyacetyl, isobutoxyacetyl, *tert.*-butoxyacetyl; or by a mono- or disaccharide radical oxidised on carbon atom 1 and/or on the terminal carbon atom to the corresponding carboxylic acid, for example, gluconoyl, glucuronoyl, saccharoyl, galactonoyl, galacturonoyl, mucoyl, mannonoyl, manno-saccharoyl, arabinoyl, ribonoyl, maltobionoyl, lactobionoyl or saccharobionoyl; or by the acyl radical of a dicarboxylic acid (containing 4—8 carbon atoms) which can form a cyclic anhydride, for example, 3-carboxypropionyl (succinoyl), 3 - carboxy - *cis* - prop - 2 - enoyl (maleinoyl), 2 - carboxy - cyclohexyl - carbonyl, phthaloyl, 2- or 3 - carboxy - pyridyl - 3 - or - 2 - carbonyl or 3 - (carboxyethylmercapto)-propionyl; or by a sulphone group.

If carboxy or sulpho radicals are contained in the radicals R, then these can also be present in the form of their alkali metal, alkaline earth metal or ammonium salts and preferably in the form of their sodium or potassium salts.

The compounds of the formula II to be used as starting materials can be used in the form of the free acid or as functional derivatives. Such functional derivatives include, for example, alkyl esters, lactones, halides, azides and anhydrides. The alkyl radicals of the ester groups can contain up to 4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl and *tert.*-butyl. As lactones, there can be used, for example, 4-butyrolactone, the 4- and 5-valerolactone and the 3 - hydroxy - 3 - methyl - 5 - valerolactone. As halides, it is preferable to use the chlorides or bromides but the fluorides and iodides can also be employed. As anhydrides, there can be used not only symmetrical anhydrides but also mixed, cyclic and Leuchs anhydrides, insofar as these can be formed. The acyloxy radical in the mixed anhydride (compounds 2 in which the hydroxyl group is replaced by acyloxy) is preferably trifluoroacetoxy, acetoxy, formyloxy, propionyloxy, butyryloxy or isobutyryloxy. Cyclic anhydrides can be derived from dicarboxylic acids, for example, from glutaric acid, maleic acid, succinic acid, cyclobutane - 1,2 - dicarboxylic acid, cyclopentane - 1,2 - dicarboxylic acid, cyclohexane-1,2 - dicarboxylic acid and phthalic acid. Leuchs anhydrides are formed, for example, from amino acids and phosgene, for example, from the 1 - amino - 1 - carboxylic acids of cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane or thiopyran, as well as from aliphatic amino acids, for example, glycine, leucine or isoleucine.

If the radical X is an arylsulphonyloxy radical, then this is preferably a phenylsulphonyloxy, *p*-tolylsulphonyloxy, naphthyl-1-sulphonyloxy or naphthyl - 2 - sulphonyloxy radical.

The preparation of the new compounds of general formula (I) and also the conversion thereof into other compounds of general formula (I) can be carried out in known manner, for example, as described in the literature (see, for example, standard references such as Houben-Weyl, Methoden der organischen Chemie, pub. Georg-Thieme-Verlag, Stuttgart) under the reaction conditions known and suitable for the individual reactions.

All the starting material needed for the preparation of the new compounds of general formula (I) can, if desired, be produced *in situ*, i.e. they are not isolated from the reaction mixture but are immediately further reacted to give the desired compounds of general formula (I).

The compounds of general formula (I) are preferably prepared by the reaction of HPI with a carboxylic acid of general formula (II) or with a functional derivative thereof. Preferred functional derivatives include carboxylic acid anhydrides, mixed carboxylic acid anhydrides, for example, *p* - fluorobenzoic acid-formic acid anhydride, carboxylic acid halides, for example, the fluorides, chlorides, bromides and iodides, and the azides. An excess of the carboxylic acid derivative can be used as solvent or the reaction is carried out in the presence of an inert solvent, for example, in an aromatic hydrocarbon, such as benzene or

toluene; in an ether, such as diisopropyl ether, tetrahydrofuran or dioxan; in a nitrile, such as acetonitrile; or in a halogenated hydrocarbon, such as dichloromethane, chloroform, carbon tetrachloride or chlorobenzene. When carrying out the acylation, it is preferable to add an inoragic or organic base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, pyridine, triethylamine or triisopropylamine. The reaction with the acid (II) itself is preferably carried out at a temperature between about 0 and 200°C. and in the case of the use of a functional derivative thereof, it is preferable to use a temperature between 0°C. and the boiling point of the solvent used and preferably a temperature approximately between 0 and 80°C. The reaction time is between about 10 minutes and 48 hours and preferably 30 minutes and 5 hours.

It is also possible to produce the carboxylic acid halides, especially the chlorides, *in situ* from the corresponding carboxylic acids (II) and halogenating reagents, for example, silicon tetrachloride, phosphorus trichloride or bromide, phosphorus oxychloride, thionyl chloride or phosphorus pentachloride, preferably in one of the abovementioned solvents and/or with the addition of one of the abovementioned organic bases. In this case, it is preferred to use temperatures between 40° and 200°C. and especially between 70° and 140°C.

The reaction of HPI with a free carboxylic acid (II) can be carried out, for example, in the presence of dicyclohexylcarbodiimide in one of the above-mentioned inert solvents or in pyridine, low temperatures (e.g. 0—20°C.) being preferred for this reaction.

It is also possible to react HPI with one of the above-mentioned lactones, in the presence or absence of a basic catalyst, for example, sodium or potassium hydride, and as a rule, in the presence of an inert solvent, for example, xylene, dimethyl formamide, dimethyl sulphoxide, sulpholane, dioxan, tetrahydrofuran or diethyl ether, at a temperature between about 0°C. and about 200°C.

As starting material, besides, racemic HPI, there can also be used one of its two optical antipodes, preferably the (-)-antipode, which, by acylation, can be converted into pharmacologically especially valuable optically-active compounds (I).

The starting materials (HPI, as well as the carboxylic acids (II)) are known or can be prepared analogously to the known compounds, using standard processes.

Compounds of general formula (I) can also be prepared by cyclising a compound of general formula (III) in the presence of a cyclising agent under conditions splitting off HX. As cyclising agents, there can be used strong bases, preferably for example, butyl lithum, potassium *tert.*-butylate, phenyl lithium, sodium hydride, alcoholates, such as sodium or potassium methylate, ethylate, propylate, isopropylate, *n*-butylate or *tert.*-butylate, amides, such as lithium diisopropylamide or the corresponding sodium or potassium amide. As a rule, the reaction is carried out in an inert solvent, for example, benzene, hexane, *tert.*-butanol, tetrahydrofuran, hexamethyl phosphoric acid triamide, dioxane, ether, dimethyl formamide, dimethyl sulphoxide or acetonitrile, if desired under nitrogen. The reaction temperature is preferably between about −20°C. and the boiling point of the solvent used. The reaction takes between about 15 minutes and about 30 hours and preferaby 10 to 14 hours.

The cyclisation can also be carried out with the use of optically-active compounds (III) as starting material, optically-active antipodes of the compounds (I) thereby being obtained.

The starting materials of the general formula (III) are obtainable according to methods known from the literature, for example, from the corresponding 1-cyano-1,2-dihydro - or 1 - cyano - 1,2,3,4 - tetrahydroisoquinolines which are substituted in the 2-position by an R—CO— radical (which has the meaning given in general formula I). These are hydrogenated in the presence of Raney nickel at an elevated temperature and pressure, with a shift of the R—CO— radical, to give the corresponding N-(1,2,3,4-tetrahydroisoquinolyl - 1 - methyl) - acylamides, which can subsequently be converted into the compounds of general formula (III) with compounds of the general formula

$$X—CH_2—CO—X,$$

for example chloroacetyl chloride.

It is also possible to obtain the compounds of general formula (I) by reduction and preferably by catalytic hydrogenation of a compound of general formula (IV). As catalysts for this purpose, there can be used the conventional catalysts known from the literature, preferably noble metal catalysts but also copper-chromium oxide catalysts, as well as nickel and cobalt catalysts. The noble metal catalysts can be used, for example, on carriers (e.g. palladium on charcoal), or as oxide catalysts (e.g. platinum oxide) or as finely-divided metal catalysts (e.g. platinum sponge). Nickel and cobalt catalysts are preferably employed as Raney metals and nickel can also be used on kieselguhr or pumice as a carrier. The hydrogenation can be carried out at pressures between about 1 and 200 ats. and at temperatures between about 0 and 200°C., preferably in the presence of a solvent, for example, an alcohol, such as methanol, ethanol, isopropanol or *tert.*-butanol, ethyl acetate, an ether, such as dioxane or tetrahydrofuran, water and/or alkali lye. If desired, the hydrogenation can also be carried out in homogeneous phase. As

catalysts for this purpose, there can be used, for example, complex compounds of heavy metals, such as soluble rhodium complexes, for example hydrido-carbonyl-tris-(triphenyl-phosphine)-rhodium.

The reduction of compounds (IV) can also be so directed that an antipode of the compounds (I) results wholly or to a preponderating extent, for example, by asymmetrical hydrogenation. As catalysts for this purpose, there can be used, for example, Raney nickel pre-treated with an asymmetric modifying reagent, for example, with aqueous solutions of optically-active hydroxy or amino acids, such as tartaric acid, citric acid, alanine, isoleucine, lysine, phenylalanine, valine or leucine.

For an asymmetric hydrogenation, there can also be used heavy metal catalysts which are applied to neutral or synthetic polymers, for example, palladium or platinum on silk or on specially prepared silica gel or polyamino acid carriers, such as are described in the literature. An asymmetric hydrogenation in homogeneous phase can be carried out with, for example, optically-active, soluble rhodium complexes. The asymmetric hydrogenation is carried out under the above-mentioned conditions, preferably at 1—3 ats. pressure and at a temperature between 20 and 50°C.

The starting compounds (IV) can be prepared, for example, by dehydrogenating a corresponding compound of general formula (I) but saturated in the 11b(1)-position, with sulphur, selenium, chloranil or another dehydrogenation agent known from the literature. A reaction of this kind is of especial interest when the compound saturated in the 11b(1)-position is present as an optically-active antipode and is less effective than the other possible antipode. In this case, the less effective antipode can be converted by dehydrogenation into the compound (IV) and subsequently hydrogenated to give the more effective saturated racemate of general formula I or, by asymmetric hydrogenation, converted substantially into the more effective antipode of general formula (I).

The radical R in a compound obtained of general formula (I) can, if desired, be converted into another radical R by methods known from and described in the literature. For example, substituents already present can be converted into other substituents.

Thus, a reducible substituent, such as the nitro group, can be reduced by catalytic hydrogenation or chemically. The catalytic hydrogenation can be carried out under the conditions given above. For carrying out the reduction, there can, for example, also be used metals (e.g. iron, zinc) with acids (e.g. hydrochloric acid or acetic acid) or stannous chloride.

An additional keto group in the acyl radical of compounds (I) can be converted into a hydroxyl group by hydrogenation or chemically. The hydrogenation is preferably carried out by the methods mentioned above. Furthermore, the keto group can be reduced with nascent hydrogen, for example, by the treatment with zinc/acid (e.g. acetic acid) or zinc/aqueous alkali metal hydroxide solution. Sodium or another alkali metal in a lower alcohol (such as ethanol, isopropanol or isoamyl alcohol) can be used. The keto groups can also be reduced with metal hydrides and preferably with complex metal hydrides which do not attack the amide group of the ring system, for example, sodium borohydride, lithium borohydride, potassium tri-(*sec.*-butyl)-borohydride or potassium trimethoxyborohydride, preferably in the presence of an inert solvent, for example of an ether, such as diethyl ether, tetrahydrofuran, dioxan, 1,2-dimethoxyethane or diglyme. Sodium borohydride can also be used in aqueous or aqueous alcoholic solution. The reaction can be carried out at a temperature between −80 and +100°C. and especially between −20°C. and the boiling point of the solvent used.

Furthermore, a keto group can be converted into a methylene group by the Wolff-Kishner method, i.e. by reaction with hydrazine and subsequent decomposition of the hydrazone formed. Furthermore, under the above-described conditions, double bonds can be hydrogenated to simple bonds or triple bonds can be hydrogenated to double or simple bonds. Using hydrogen/palladium, an N-oxide group in the radical R can also be reduced according to known methods to the corresponding tertiary amine.

A compound (I) which contains a tertiary nitrogen atom in the acyl radical con be converted into the corresponding N-oxide by reaction with an inorganic or organic peroxide, for example hydrogen peroxide (preferably a 30% aqueous solution or a mixture of hydrogen peroxide with formic acid), peracetic acid, perbenzoic acid, 3-chloro-perbenzoic acid or *tert.*-butyl hydro-peroxide. As solvents for the organic peroxides, there can be used, for example, methylene chloride, chloroform or an alcohol, such as methanol or isopropanol. The reaction can be carried out at a temperature between about 0 and 50°C. and preferably at ambient temperature. The reaction time can be between 1 and 48 hours.

Compounds (I) which contain a mercapto group in the radical R can be oxidised to the corresponding sulpho compounds with, for example, nitric acid. Analogously, the corresponding alkylthio groups can be converted into sulphones or sulphoxides with, for example, nitric acid, an aqueous solution of hydrogen peroxide or 3-chloroperbenzoic acid.

Alcohol groups in the radical R can be converted into carbonyl groups, for example by oxidation with manganese dioxide or chromic acid.

Compounds (I) which contain, as sub-

stituents, one or more free hydroxy, mercapto, amino or monoalkylamino groups, can be alkylated to the corresponding alkoxy, alkylthio, monoalkylamino, dialkylamino or trialkylammonium compounds or can be acylated to the corresponding acyl compounds.

For the O- and S-alkylation, the starting materials are preferably first converted into the corresponding salts by addition of a base, for example of an aqueous solution of sodium hydroxide, potassium hydroxide or potassium carbonate. Examples of alkylation agents which can be used include alkyl halides, such as methyl chloride, bromide or iodide, ethyl chloride, bromide or iodide, the corresponding dialkyl sulphuric acid or alkylsulphonic acid esters, such as dimethyl sulphate, diethyl sulphate or methyl *p*-toluenesulphonate, or diazo compounds, such as diazomethane. Amino compounds can also be alkylated reductively with formaldehyde or acetaldehyde in the presence of hydrogen and a catalyst or in the presence of formic acid. As solvent, there can be used, for example, water or an aqueous sodium hydroxide solution; an alcohol, such as methanol, ethanol or *n*-butanol; a hydrocarbon, such as benzene or xylene; an ether, such as tetrahydrofuran or dioxan; or an amide, such as dimethyl formamide. The alkylation is preferably carried out at a temperature between about −10 and about +150°C. and especially between ambient temperature and the boiling temperature of the solvent used.

A corresponding acylation is preferably carried out with a carboxylic acid or carboxylic acid derivative, for example, under the conditions described above for the acylation of HPI. Acylation can also be carried out with ketenes, preferably in an inert solvent, for example, ether, dichloromethane, chloroform, benzene or toluene, possibly with the addition of an acidic catalyst, for example sulphuric acid or *p* - toluene - sulphonic acid. Thus, for example, from 2 - (4 - hydroxybenzoyl)-HPI and ketene, there is obtained 2 - (4-acetoxybenzoyl)-HPI.

By the reaction of compounds obtained of general formula (I), which contain a primary or secondary amino group in the radical R, with a derivative of sugar under the above-described conditions, there can be prepared compounds, the amino group of which in the radical R is protected by a sugar acid. As sugar derivatives, there can be used, for example, the lactones of the sugars, such as gluconic acid lactone or glucuronic acid lactone.

Amino groups in the radical R can also be reacted with a sugar acid or with a functional derivative thereof, the other hydroxyl groups of which are protected with, for example, benzyl groups, whereafter the protective groups are again split off, for example, by hydrogenation. Thus, 2 - (4 - gluconoylaminobenzoyl)-HPI can be prepared, for example, by the reaction of 2 - (4 - aminobenzoyl) - HPI with 2,3,4,5,6 - penta - O - benzyl - gluconoyl chloride and subsequent hydrogenolysis of the benzyl groups in the resultant 2 - [4-(2,3,4,5,6 - penta - O - benzyl - gluconoylamino) - benzoyl] - HPI.

Compounds (I), the amino group(s) of which in the radical R are protected by one (or more) sulpho group(s) can be obtained from compounds (I) obtained with one (or more) free amino group(s) in the radical R by reaction with chlorosulphonic acid, for example, under the reaction conditions described above for the reaction of HPI with acid halides.

Furthermore, it is possible to convert acyloxy (e.g. formyloxy, acetoxy, trifluoroacetoxy, phthaloyloxy or another easily saponifiable group), acylmercapto or alkoxycarbonyl radicals (e.g. methoxycarbonyl or ethoxycarbonyl) in compounds obtained of general formula (I) into hydroxyl, mercapto or carboxy groups by treatment with solvolysing agents. For this purpose, there can be used acids, such as hydrochloric acid or acetic acid, or, preferably, bases, such as sodium or potassium carbonate or calcium, barium, sodium or potassium hydroxide, for example in aqueous methanol. Mild reaction conditions are preferably used in order not to attack the acid amide group. Generally, the reaction is carried out at a temperature between about −40 and +90°C. for a period of 2 to 50 hours.

Cyano groups in compounds (I) can be hydrolysed to carbamoyl groups in an acidic medium (e.g. with hydrochloric or sulphuric acid in water, methanol, ethanol, aqueous dioxan or acetic acid) or in an alkaline medium (e.g. with potassium hydroxide in aqueous ethanol or in cyclohexanol) medium. It is also possible to use hydrogen peroxide in alkaline solution, generally at temperatures between ambient temperature and 80°C. for a period of 1—5 hours.

Compounds (I) in which an amino group in the acyl radical is protected in the form of a Schiff base, can be converted hydrogenolytically into the corresponding secondary amines. The Schiff bases are thereby preferably derived from aldehydes, for example formaldehyde, benzaldehyde or glyoxylic acid, or also from ketones, such as acetone. For the hydrogenation, there can be used, for example, hydrogen in the presence of platinum or Raney nickel at ambient temperature under atmospheric pressure.

Benzylamino compounds can be split to give the corresponding primary amines, for example with hydrogen in the presence of a noble metal catalyst, such as palladium.

It is also possible to convert Schiff bases obtained into the corresponding bisulphite adducts by reaction with bisulphite. The bisulphite adducts can also be obtained by direct reaction of an aldehyde-bisulphite addition

product with a compound (I) which has a free amino group in the radical R.

Urethane groups in the radical R of compounds (I), for example N-ethoxycarbonyl or N-benzoyloxycarbonyl groups, can be split off with, for example, hydrogen chloride in acetic acid.

From thiourethane groups which are contained in the radical R of compounds (I), the corresponding amino groups can be liberated with an alkali metal acetate or lead diacetate in an alcohol, for example methanol or ethanol, or with an alkali metal hydroxide solution in the presence of lead dihydroxide or lead carbonate.

In principle, as protective groups for an amino group in the acyl radical of the compounds (I), there can be present all those which are successfully employed in peptide syntheses. Correspondingly, the methods known from the literature for splitting off those protective groups can also be employed.

An alkylamino substituent in a compound (I) can also be converted into a 1-alkylhydrazino substituent, for example by reaction with nitrous acid and reduction of the nitrosoamino compound obtained with nascent hydrogen (e.g. from zinc/acetic acid) or with stannous chloride.

Furthermore, keto groups in the radical R of compounds (I) can be converted into amino groups. Thus, for example, ketones can be reacted with hydroxylamine or with hydrazine and the resultant oximes or hydrazones hydrogenated, for example in the presence of Raney nickel at about 1—50 ats. According to another method, ketones can be hydrogenated in the presence of ammonia or of primary or secondary amines, primary, secondary or tertiary amines (I) thereby being obtained. The reaction is preferably carried out at pressures between 1 and 200 ats. and at a temperature between −40 and 150°C. in, for example, methanol, ethanol, isopropanol, tetrahydrofuran or liquid ammonia.

Furthermore, keto groups in compounds (I) can be converted, according to conventional methods, into CF_2 groups, for example with sulphur tetrafluoride or phenyl sulphur trifluoride, in the presence of hydrofluoric acid or also with carbonyl difluoride in the presence of pyridine. The reaction is preferably carried out in an autoclave at a slight overpressure and an inert solvent, for example methylene chloride, chloroform or tetrahydrofuran, at a temperature between 0 and 150°C.

It is also possible to split off alkoxy or alkylthio groups present in compounds (I) to give hydroxyl or mercapto groups. Reaction conditions must thereby be selected under which the acid amide groupings remain intact. It is preferable to use a Lewis acid, such as boron tribromide, in an inert solvent, such as dichloromethane, chloroform or carbon tetrachloride, at a temperature between about −40° and +50°C.

Compounds (I) which contain one or more amino groups can be converted into the corresponding diazonium compounds by conventional diazotisation methods, whereafter the diazonium group can be replaced, for example, by fluorine, chlorine, bromine, iodine, cyano, hydroxyl, mercapto, O-alkyl or S-alkyl. The diazotisation of the amino compound can be carried out, for example, in aqueous sulphuric acid, hydrochloric acid, hydrobromic acid or tetrafluoroboric acid by the addition of an inorganic nitrite, preferably of sodium or potassium nitrite, at a temperature between about −20 and +10°C. It is also possible to use an organic nitrite, such as *n*-butyl nitrite, *n*-amyl nitrite or isoamyl nitrite, at a temperature between −20 and +5°C. in an inert organic solvent, such as diethyl ether, tetrahydrofuran or dioxan.

For the introduction of a fluorine atom, diazotisation is carried out, for example, in anhydrous hydrofluoric acid with subsequent heating or the diazonium salts are reacted with tetrafluoroboric acid to give the sparingly soluble diazonium tetrafluoroborates. These can be isolated and converted themally, for example, by heating in an inert solvent, into the desired fluoro compounds. However, the diazonium tetrafluoroborates, especially those of heterocyclic compounds, can, without isolation, be irradiated in aqueous suspension with a mercury lamp and then give the desired fluoro compounds. The diazonium group can be replaced by chlorine or bromine, preferably in hot aqueous solution, in the presence of cuprous chloride or bromide. The replacement of a diazonium iodide group for iodine even takes place by slight warming, whereby cuprous iodide, bromide or chloride can be added. The replacement of the diazonium group by a cyano group takes place, for example, in the presence of cuprous cyanide and an alkali metal cyanide, for example sodium or potassium cyanide, at about 0 to +50°C. The diazonium salt grouping can also be replaced by an alkoxy radical, for example, by heating in aqueous alcoholic solution. Replacement by a mercapto group is preferably carried out by the reaction of the diazonium compound with an alakli metal xanthogenate, for example sodium ethyl xanthogenate, and subsequent alkaline saponification.

The diazonium compounds can also be coupled with appropriate coupling components to give corresponding diazo dyestuffs. As coupling components, it is especially preferred to use benzene compounds which contain activating substituents, such as amino, alkylamino, dialkylamino, hydroxy or alkoxy groups, and, in addition, can also contain further substituents, such as carboxy, halogen (preferably fluorine or chlorine), sulpho or alkyl groups.

Basic compounds (I) can, if desired, be converted into their physiologically compatible acid-addition salts. For this purpose, there can be used, for example, inorganic or organic acids, such as aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic or sulphonic acids, for example, mineral acids, such as hydrochloric, hydrobromic or hydriodic acid, sulphuric acid, nitric acid, phosphoric acids, such as orthophosphoric acid or sulphamic acid; organic acids, such as formic acid, acetic, propionic, butyric, pivalic, diethylacetic, oxalic, malonic, succinic, pimelic, fumaric, maleic, citric, gluconic, lactic, tartaric, malic, benzoic, salicylic, phenylpropionic, ascorbic, isonicotinic, methanesulphonic, ethanedisulphonic, 2 - hydroxyethanesulphonic (isethionic), *p*-toluene-sulphonic, naphthalene-mono- or disulphonic acids (e.g. naphthalene-1- or -2-sulphonic or naphthalene-1,5- or -2,6-disulphonic acid).

Compounds (I) which contain a free carboxyl or sulpho group can be converted, by reaction with a base, into one of their physiologically compatible metallic or ammonium salts. Examples of such salts include the sodium, potassium, magnesium, calcium and ammonium salts, as well as substituted ammonium salts, such as dimethyl and diethyl ammonium, cyclohexyl ammonium, dicyclohexyl ammonium, N - alkyl - or N - aryl - substituted piperazinium salts (such a methyl - piperazinium and ethyl-piperazinium salts), as well as the N,N-dibenzyl-ethylene-diammonium salts.

On the other hand, basic compounds (I) can be liberated from their acid addition salts by treatment with bases, such as sodium or potassium hydroxide or sodium or potassium carbonate, and acidic compounds (I) from their metallic and ammonium salts by treatment with acids, especially with mineral acids, such as dilute hydrochloric or sulphuric acid.

Compounds (I) which contain a primary, secondary or tertiary amino group can be converted into their physiologically compatible quaternary ammonium salts by treatment with quaternising alkylation agents, such as methyl iodide, dimethyl sulphate or ethyl halides.

Optically-active compounds of general formula (I) are preferably obtained by using starting materials which are already optically-active. Antipodes of HPI or those of compound (III) are preferably used. However, it is also possible to resolve racemates obtained of general formula (I) into their optical antipodes, chemical separation methods thereby being preferred. Thus, for example, a racemate of general formula (I) can be reacted with an optically-active adjuvant and the diastereomeric mixture obtained resolved in an appropriate manner. Thus, for example, a racemate of general formula (I) which contains an acidic group (e.g. a carboxyl group) can be reacted with an optically-active base or a racemate (I) which contains a basic group (e.g. an amino group) can be reacted with an optically-active acid. Optically-active bases include optically-active amines, such as quinine, cinchonidine, brucine, cinchonine, hydroxyhydrindamine, morphine, 1-phenylethylamine, 1-naphthylethylamine, quinidine or strychnine, basic amino acids, such as lysine or arginine, or amino acid esters. On the other hand, as optically-active acids, there can be used the (+) and (−) forms of tartaric acid, dibenzoyl-tartaric acid, diacetyltartaric acid, camphoric acid, β-camphor-sulphonic acid, mandelic acid, malic acid, 2-phenyl-butyric acid, dinitrodiphenic acid, lactic acid or quinic acid. The diastereomeric mixtures obtained can subsequently be separated by selective crystallisation or by manual selection. Finally, the isolated diastereomeric compounds can be decomposed hydrolytically to the desired optically-active compounds of general formula (I).

The compounds (I) act well against cestodes and trematodes. Thus, they can be used against the following cestodes (arranged according to hosts):

1. *Ruminants: Moniezia, Stilesia, Avitellina, Thysanosoma, Thysaniezia,* hydatids of *Taenia* sp., *Coenurus cerebralis* and *Echinococci* hydatids;
2. *Ungulates: Anoplocephala;*
3. *Rodents: Hymenolepis* (especially *H. nana* and *H. diminuta)*;
4. *Birds: Davainea, Raillietina* and *Hymenolepis*;
5. *Canines and felines: Taenia* (especially *T. hydatigena, T. pisiformis; T.taeniaeformis, T. ovia, T.serialis, T. cervi* and *T.multiceps*), *Dipylidium* (especially *D. caninum*) and *Echinococcus* (especially *E. granulosus* and *E. multilocularis)*;
6. *Humans: Taenia* (especially *T. solium, T. saginata* and *T. serialis), Hymenolepis* (especially *H. nana* and *H. diminuta), Drepanidotaenia, Dipylidium, Diplopylidium, Coenurus* (especially *C. cerebralis), Diphyllobothium* (especially *D. latum)* and *Echinococcus* hydatids (especially of *E. granulosus* and *E. multiloculatis*).

The trematodes which are important to combat in human and veterinary medicine include those of the families of the *Schistosomidae,* especially of the genus *Schistosoma (Sch. mansoni, Sch. haematobium* and *Sch. japonicum*). Furthermore, the genuses *Fasciola, Dicrocoelium, Clonorchis, Opisthorchis, Paragonimus, Paramphistomum, Echinostoma* and the like can possibly also be influenced.

The compounds (I) can, *inter alia,* be used in the following host and/or intermediate host organisms for combating cestodes or trematodes and/or their larvae: humans, the types of monkeys, as well as the most important domestic and wild animals, for example canines, such as dogs and foxes; felines,

such as cats; ungulates, such as horses, asses and donkeys; cervides, such as roe, red and fallow deer; chamois; rodents; ruminants, such as cows, sheep and goats; birds, such as hens and ducks; pigs; and fish.

Habitats of the influencable parasites or of their larvae include especially the gastro-intestinal tract, for example the stomach, intestines, pancreas and bile duct. However, various other organs include, for example, the liver, kidneys, lungs, heart, spleen, lymph nodes, brain, spinal cord and testes, the abdominal cavity, connective tissue, musculature, peritoneum, pleura and diaphragm and the blood vessels. Thus, with good compatibility, the compounds (I) act, for example, against *Schistosoma sp.* in the blood vessel system, *Hymenolepis microstoma* in the bile duct and *T. hydatigena* hydatids in the liver.

The compounds (I) can be used as such or admixed with pharmaceutically acceptable inert carriers. Carriers of this type can be, for example, capsules, solid diluents or fillers, sterile aqueous media and/or various non-toxic organic solvents.

The forms of administration which can be used include, *inter alia*, tablets and dragees (which can contain the active material in depot form), effervescent tablets, capsules, granulates, aqueous suspensions, injectable solutions, emulsions and suspensions, elixirs, syrups and pastes. The formulations for this purpose can be prepared in known manner, for example, by the addition of the active materials to solvents and/or carrier materials, possibly with the use of emulsifying agents and/or dispersion agents. As adjuvant materials, there can be used, for example, water, non-toxic organic solvents (e.g. paraffins or alcohols, such as glycerol or polyethylene glycol), vegetable oils (e.g. sesame oil), solid carrier materials, such as natural or synthetic mineral powders (e.g. talc or highly-dispersed silicic acid), sugars, emusifiers (e.g. ionic or non-ionic), dispersions agents (e.g. methyl cellulose and polyvinyl pyrrolidone) and/or lubricants (e.g. magnesium stearate). Tablets can also contain additives, such as sweetening agents, sodium citrate, calcium carbonate and dicalcium phosphate, together with additional materials, such as starch, gelatine or the like. Aqueous suspensions and/or elixirs can also contain flavour improvers or colouring materials. The compounds (I) can possibly also be administered without or almost without adjuvant materials, e.g. in capsules.

The administration of the active materials (I) preferably takes place orally but a parenteral, especially subcutaneous, as well as dermal administration, is also possible.

For combating adult cestodes, it is advantageous to administer the active materials one or more times daily in amounts of 0.01 to 250 and preferably of about 0.5 to 100 mg./kg., orally or subcutaneously. For combating the corresponding tape worm larvae (hydatids) or for combating *Schistosomes*, larger amounts of active material might be necessary.

In the case of the administration of comparatively large amounts of active material, smaller individual doses can also be spread out over the day. Thus, instead of 1000 mg., 5 separate doses each of 200 mg. can be administered. In the case of veterinary medicine, administration with the food can also be used, pre-mixes to be added preferably being prepared.

It might be necessary to deviate from the given amounts, depending upon the body weight or the nature of the administration route but also because of the species and their individual behaviour towards the medicament or the nature of its formulation or the point of time or interval at which the administration takes place. Thus, in some cases, it might be sufficient to use less than the above-mentioned minimum amount, whereas, in other cases, the above-mentioned upper limit must be exceeded.

Depending upon the nature of administration, the ratio between the compounds (I) and the carrier and/or adjuvant material used can be varied considerably. If a compound (I) is administered, for example, in a tablet or dragee, then about 0.01 to 2500 mg. active substance can be mixed with about 1 to 10,000 mg. adjuvant material. If, on the other hand, a compound (I) is formulated as pre-mixture for a medicinal feed, then, per 1 kg. carrier or adjuvant material, there can be used about 0.1 — 400 g. compound (I). When formulated as an injection liquid, a solution of 1 litre liquid can contain, depending upon the nature of the solubilising agent used, about 0.5 to 100 g. of compound (I). Similarly, in 1 litre of syrup, there can be dissolved or suspended about 0.5—250 g. of compound (I).

The compounds (I) can also be present in the formulations in admixture with other active materials. Thus, for the achievement of a broader spectrum of activity, it can be useful to add an active material which acts against nematodes, for example thiabendazol [2-(4-thiazolyl)-benzimidazole] or piperazine (or a piperazine derivative, such as N - methyl-piperazine). It is also possible to administer a mixture of two or more compounds of general formula (I).

The anthelmintic action of the compounds (I) is described in more detail in the following Examples:

A. *Pharmacological examples.*

The following compounds (I) were tested:
Active material

A 2-(4-aminobenzoyl)-HPI
B 2-(3-fluorobenzoyl)-HPI
C 2-cyclohexylcarbonyl-HPI
D 2-(4-tetrahydropyranylcarbonyl)-HPI
E 2-(3-thienylcarbonyl)-HPI

F 2-(4-nitrobenzoyl)-HPI
G 2-nicotinoyl-HPI
H 2-isobutyryl-HPI

As comparison preparations, there were used:
Quinacrin [2 - methoxy - 6 - chloro - 9 - [(1-methyl - 4 - diethylaminobutyl) - amino]-acridine],
Niclosamide [N - (2 - chloro - 4 - nitrophenyl) - 5 - chlorosalicylamide],
Dichlorophen (2,2' - dihydroxy - 5,5' - dichlorodiphenylmethane),
Lucanthone [1 - (2 - diethylaminoethylamino) - 4 - methylthioxanthone hydrochloride],
Niridazole [1 - (5 - nitro - 2 - thiazolyl)-imidazolidin-2-one],
Stibophen [sodium antimony - bis - (pyrocatechol - 2,4 - disulphonate)].

Example a)
Hymenolepis nana, adults, larvae/mouse
Hymenolepis microstoma, adults/mouse
Hymenolepis diminuta/rat

Experimental animals experimentally infected with *H. nan*, *H. microstoma* or *H. diminuta* were treated 1—3 days after infection (larvae) or after expiry of the prepotence of the parasites. The active material was administered orally or subcutaneously as an aqueous suspension.

The degree of action of the preparation was determined, after section, by counting the number of worms remaining in the experimental animals, in comparison with untreated animals, followed by calculation of the percentage of the action.

TABLE 1

Active material	parasite	effective minimum dose in mg/kg (parasite reduction >90%)
A	*H. nana*–adults	20
	H. nana–larvae	100
	H. microstoma	50
	H. diminuta	25
B	*H. nana*–adults	50
	H. diminuta	100
C	*H. nana*–adults	20
	H. microstoma	100
	H. diminuta	25
D	*H. nana*–adults	50
	H. diminuta	50
E	*H. nana*–adults	250
	H. diminuta	250
F	*H. nana*–adults	50
	H. diminuta	50
G	*H. nana*–adults	20
H	*H. nana*–adults	50
Quinacrin	*H. diminuta*	>1000
Niclosamide	*H. nana*–adults	500
	H. nana–larvae	ineffective
	H. microstoma	500
Dichlorophen	*H. nana*–adults	>1000
	H. diminuta	500

Example b)

Taenia taeniaeformis larvae (hydatids)/mouse

Mice experimentally infected with *Taenia taeniaeformis* larvae were treated about 2—5 months after infection. The active material was administered orally as an aqueous suspension.

The degree of action of the preparation was determined, after section, by counting the number of living and dead larvae in comparison with untreated control animals and thereafter calculating the percentage of the action.

TABLE 2

active material	effective minimum dose in mg/kg (parasite reduction >90%)
A	100
Quinacrin	ineffective
Niclosamide	ineffective

Example c)
Taenia spec./dog

Dogs infected experimentally or naturally with *Taenia hydatigena* or *Taenia pisiformis* were treated after the expiry of the prepotence of the parasites. The active material was administered orally in gelatine capsules.

TABLE 3

active material	effective minimum dose in mg/kg (parasite reduction >90%)
A	10
B	25
C	10
D	10
E	10
H	10
Niclosamide	50

The degree of action was determined by counting the worms expelled after the treatment and those remaining in the experimental animal, after section, and calculating the percentage of the worms expelled.

Example d)
Echinococcus multilocularis/dog

Dogs experimentally infected with *Echinococcus multilocularis* were treated between the 25th and 29th day after infection. The active material was administered orally as pure active material in gelatine capsules. The degree of action was calculated analogously to Example a).

TABLE 4

active material	effective minimum dose in mg/kg (parasite reduction >90%)
A	50
B	50
C	50
Niclosamide	insufficiently effective to ineffective

Example e)
Schistosoma mansoni/mouse

Mice infected experimentally with *Schistosoma mansoni* were treated after the expiry of the prepotence of the parasites. The active material was administered orally in aqueous suspension. After section of the experimental animals, the effect was determined by counting the surviving and the dead parasites.

TABLE 5

active material	effective minimum dose in mg/kg (parasite reduction >90%)
A	100
B	100
C	100
D	500
H	500
Niridazole	500
Stibophen	>1000

In the following Examples, which are given for the purpose of illustrating the present invention, $[\alpha]$ means $[\alpha]_D^{20}$ in chloroform.

Example 1.

3.71 g. 4-nitrobenzoyl chloride in 50 ml. chloroform are added dropwise at 20°C. to 4.04 g. (±)-HPI and 2.8 ml. triethylamine in 50 ml. chloroform. After one hour, the reaction mixture is shaken with dilute hydrochloric acid and water. After drying and evaporating, (±)-2-(4-nitrobenzoyl)-HPI is obtained which, after recrystallisation from methanol, melts at 212—213°C.

The following compounds are prepared analogously from the appropriate carboxylic acid chlorides:—

2-acetyl-HPI; m.p. 139°C.
2-propionyl-HPI;
2-*n*-butyryl-HPI;
2-isobutyryl-HPI; m.p. 120°C.;
2-*n*-valeryl-HPI;
2-isovaleryl-HPI;
2-(2-methylbutyryl)-HPI; m.p. 95—96°C.;
2-trimethylacetyl-HPI; m.p. 150°C.;
2-*n*-hexanoyl-HPI;
2-(2-methyl-n-valeryl)-HPI; m.p. 121°C.;
2-(3-methyl-*n*-valeryl)-HPI;
2-(4-methylvaleryl)-HPI;
2-(2-ethyl-*n*-butyryl)-HPI; m.p. 121°C.;
2-(2,2-dimethyl-*n*-butyryl)-HPI;
2 - (3,3 - dimethyl - *n* - butyryl) - HPI; m.p. 113°C.;
2-heptanoyl-HPI; m.p. 90—91°C.;
2-(2,2-dimethylvaleryl)-HPI; m.p. 129°C.;
2-octanoyl-HPI;
2-(2-*n*-propyl)-hexanoyl)-HPI;
2-decanoyl-HPI;
2-(2-*n*-butylhexanoyl)-HPI; m.p. 96°C.;
2-undecanoyl-HPI;
2-hexadecanoyl-HPI; m.p. 101—102°C.;
2-octadecanoyl-HPI;
2-trifluoroacetyl-HPI;
2-chloroacetyl-HPI;
2-dichloroacetyl-HPI; m.p. 151—152°C.;
2-trichloroacetyl-HPI; m.p. 184—185°C.;
2-(3-chloropropionyl)-HPI;
2 - tris - (chloromethyl) - acetyl - HPI; m.p. 133—135°C.;
2-(2-acetoxyacetyl)-HPI;
2-(2-methoxyacetyl)-HPI; m.p. 135°C.;
2-(2-ethoxyacetyl)-HPI;
2-dimethylaminoacetyl-HPI;
2-diethylaminoacetyl-HPI;
2-methyl-ethylaminoacetyl-HPI;
2-(2-dimethylamino-propionyl)-HPI;
2-(2-diethylamino-propionyl)-HPI;
2-(3-dimethylamino-propionyl)-HPI;
2-(3-diethylamino-propionyl)-HPI;
2-(2-dimethylamino-*n*-butyryl)-HPI;
2-(2-diethylamino-*n*-butyryl)-HPI;
2-(4-dimethylamino-*n*-butyryl)-HPI;
2-(4-diethylamino-*n*-butyryl)-HPI;
2-(2-dimethylamino-*n*-valeryl)-HPI;
2-(2-diethylamino-*n*-valeryl)-HPI;
2-(5-dimethylamino-*n*-valeryl)-HPI;
2-(5-diethylamino-*n*-valeryl)-HPI;
2-(2-dimethylamino-*n*-hexanoyl)-HPI;
2-(6-dimethylamino-*n*-hexanoyl)-HPI;
2-(6-diethylamino-*n*-hexanoyl)-HPI;
2-(2-phenylacetyl)-HPI; m.p. 123—124°C.;
2-(2-hydroxy-2-phenylacetyl)-HPI;
2 - (2 - acetoxy - 2 - phenylacetyl) - HPI; m.p. 101—102°C.;
2-phenoxyacetyl-HPI;
2-(4-fluorophenoxyacetyl)-HPI;
2-(3-chlorophenoxyacetyl)-HPI;
2-(4-chlorophenoxyacetyl)-HPI; m.p. 159—160°C.;
2-[3-(4-fluorophenoxy)-propionyl]-HPI;
2-[3-(3-chlorophenoxy)-propionyl]-HPI;
2-[3-(4-chlorophenoxy)-propionyl]-HPI;
2 - (thienyl - 2 - mercaptoacetyl) - HPI; m.p. 89—90°C.;
2-(thienyl-3-mercaptoacetyl)-HPI;
2-crotonoyl-HPI;
2-methacryloyl-HPI;
2-vinylacetyl-HPI;
2-cinnamoyl-HPI; m.p. 152°C.
2-phenylpropioloyl-HPI; m.p. 155°C.;
2-phenoxycarbonyl-HPI; m.p. 136—137°C.;
2-ethoxalyl-HPI; m.p. 126°C.;
2-cyclopropyl-carbonyl-HPI; m.p. 148°C.;
2-(2-acetoxycyclopropyl-carbonyl)-HPI;
2-(2-fluorocyclopropyl-carbonyl)-HPI;
2 - cyclobutyl - carbonyl - HPI; m.p. 154—155°C.;
2-(2-ketocyclobutyl-carbonyl)-HPI;
2-(3-ketocyclobutyl-carbonyl)-HPI;
2-(2-fluorocyclobutyl-carbonyl)-HPI;
2-(3-fluorocyclobutyl-carbonyl)-HPI;
2-(2-chlorocyclobutyl-carbonyl)-HPI;
2-(3-chlorocyclobutyl-carbonyl)-HPI;
2-(2-methylcyclobutyl-carbonyl)-HPI;
2-(3-methylcyclobutyl-carbonyl)-HPI;
2-(2,2-difluorocyclobutyl-carbonyl)-HPI;
2-(3,3-difluorocyclobutyl-carbonyl)-HPI;
2-(1-acetoxycyclobutyl-carbonyl)-HPI;
2-(2-acetoxycyclobutyl-carbonyl)-HPI;
2-(3-acetoxycyclobutyl-carbonyl)-HPI;
2 - (1 - dimethylaminocyclobutyl - carbonyl)-HPI;
2 - (2 - dimethylaminocyclobutyl - carbonyl)-HPI;
2 - (3 - dimethylaminocyclobutyl - carbonyl)-HPI;
2 - (2 - methoxycarbonylcyclobutyl - carbonyl)-HPI;
2 - (2 - ethoxycarbonylcyclobutyl - carbonyl)-HPI;
2 - (3 - methoxycarbonylcyclobutyl - carbonyl)-HPI;
2 - (3 - ethoxycarbonylcyclobutyl - carbonyl)-HPI;
2-cyclopentyl-carbonyl-HPI; m.p. 127°C.;
2-(2-ketocyclopentyl-carbonyl)-HPI;
2-(3-ketocyclopentyl-carbonyl)-HPI;
2-(1-acetoxycyclopentyl-carbonyl)-HPI;
2-(2-acetoxycyclopentyl-carbonyl)-HPI;
2-(3-acetoxycyclopentyl-carbonyl)-HPI;
2-(2-fluorocyclopenyl-carbonyl)-HPI;
2-(3-fluorocyclopentyl-carbonyl)-HPI;
2-(2,2-difluorocyclopentyl-carbonyl)-HPI;
2-(3,3-difluorocyclopentyl-carbonyl)-HPI;
2-(2-chlorocyclopentyl-carbonyl)-HPI;
2-(3-chlorocyclopentyl-carbonyl)-HPI;
2-(2-methylcyclopentyl-carbonyl)-HPI;
2-(3-methylcyclopentyl-carbonyl)-HPI;
2 - (1 - dimethylaminocyclopentyl - carbonyl)-HPI;
2 - (2 - dimethylaminocyclopentyl - carbonyl)-HPI;
2 - (3 - dimethylaminocyclopentyl - carbonyl)-HPI;

2 - (2 - methoxycarbonylcyclopentyl - carbonyl)-HPI;
2 - (2 - ethoxycarbonylcyclopentyl - carbonyl)-HPI;
2 - (3 - methoxycarbonylcyclopentyl - carbonyl)-HPI;
2 - (3 - ethoxycarbonylcyclopentyl - carbonyl)-HPI;
2-cyclohexylcarbonyl-HPI; m.p. 136—138°C.
2-(1-cyclohexenyl-carbonyl)-HPI;
2-(2-cyclohexenyl-carbonyl)-HPI;
2 - (3 - cyclohexenyl - carbonyl)-HPI; m.p. 126°C.
2-(2-ketocyclohexyl-carbonyl)-HPI;
2-(3-ketocyclohexyl-carbonyl)-HPI;
2 - (4 - ketocyclohexyl - carbonyl) - HPI; m.p. 154°C.;
2-(1-acetoxycyclohexyl-carbonyl)-HPI;
2-(2-acetoxycyclohexyl-carbonyl)-HPI;
2-(3-acetoxycyclohexyl-carbonyl)-HPI;
cis - 2 - (4 - acetoxycyclohexyl - carbonyl)-HPI; m.p. 130—132°C.;
2-(1-formamidocyclohexyl-carbonyl)-HPI;
2-(2-formamidocyclohexyl-carbonyl)-HPI;
2-(3-formamidocyclohexyl-carbonyl)-HPI;
2-(4-formamidocyclohexyl-carbonyl)-HPI;
2 - (1 - dimethylaminocyclohexyl - carbonyl)-HPI;
2 - (2 - dimethylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - dimethylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - dimethylaminocyclohexyl - carbonyl)-HPI;
2 - [2,4 - bis - (dimethylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,4 - bis - (dimethylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,5 - bis - (dimethylamino) - cyclohexyl-carbonyl]-HPI;
2 - (1 - diethylaminocyclohexyl - carbonyl)-HPI;
2 - (2 - diethylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - diethylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - diethylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - methylethylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - methylethylaminocyclohexyl - carbonyl)-HPI;
2-(2-fluorocyclohexyl-carbonyl)-HPI;
2-(3-fluorocyclohexyl-carbonyl)-HPI;
2-(4-fluorocyclohexyl-carbonyl-HPI;
2-(2,2-difluorocyclohexyl-carbonyl)-HPI;
2-(3,3-difluorocyclohexyl-carbonyl)-HPI;
2-(4,4-difluorocyclohexyl-carbonyl)-HPI;
2-(2-chlorocyclohexyl-carbonyl)-HPI;
2-(3-chlorocyclohexyl-carbonyl)-HPI;
2-(4-chlorocyclohexyl-carbonyl)-HPI;
2-(2-bromocyclohexyl-carbonyl)-HPI;
2-(3-bromocyclohexyl-carbonyl)-HPI;
2-(4-bromocyclohexyl-carbonyl)-HPI;
2-(2-methylcyclohexyl-carbonyl)-HPI;
2-(3-methylcyclohexyl-carbonyl)-HPI;
2-(4-methylcyclohexyl-carbonyl)-HPI;
2 - (2 - methoxycarbonylcyclohexyl - carbonyl)-HPI;
2 - (3 - methoxycarbonylcyclohexyl - carbonyl)-HPI;
2 - (4 - methoxycarbonylcyclohexyl - carbonyl)-HPI;
2 - (2 - ethoxycarbonylcyclohexyl - carbonyl)-HPI;
2 - (3 - ethoxycarbonylcyclohexyl - carbonyl)-HPI;
2 - (4 - ethoxycarbonylcyclohexyl - carbonyl)-HPI;
2-cycloheptylcarbonyl-HPI; m.p. 91°C.;
2 - (4 - dimethylaminocycloheptyl - carbonyl)-HPI;
2 - (4 - diethylaminocycloheptyl - carbonyl)-HPI;
2-(4-fluorocycloheptyl-carbonyl)-HPI;
2-(4-chlorocycloheptyl-carbonyl)-HPI;
2-cyclooctylcarbonyl-HPI; m.p. 109°C.;
2-cyclononylcarbonyl-HPI;
2-cyclodecylcarbonyl-HPI;
2 - cycloundecylcarbonyl - HPI; m.p. 150—151°C.;
2-cyclododecylcarbonyl-HPI;
2-bicyclo[2,2,1]heptyl-2-carbonyl-HPI;
2-bicyclo[2,2,2]-octyl-2-carbonyl-HPI;
2-(adamantyl-carbonyl)-HPI; m.p. 159—160°C.;
2-(2-methylbenzoyl)-HPI;
2-(3-methylbenzoyl)-HPI; m.p. 124°C.;
2 - (4 - methylbenzoyl) - HPI; m.p. 183—184°C.;
2-(4-ethylbenzoyl)-HPI;
2-(4-*n*-propylbenzoyl)-HPI;
2-(4-isopropylbenzoyl)-HPI;
2-(4-*tert.*-butylbenzoyl)-HPI; m.p. 198°C.;
2-(4-phenylbenzoyl)-HPI;
2-(3,4-dimethylbenzoyl)-HPI;
2-(3,5-dimethylbenzoyl)-HPI;
2-(3,4-diethylbenzoyl)-HPI;
2-(3,5-diethylbenzoyl)-HPI;
2-(2-fluorobenzoyl)-HPI; m.p. 129°C.;
2 - (3 - fluorobenzoyl) - HPI; m.p. 164—166°C.;
2 - (4 - fluorobenzoyl) - HPI; m.p. 181—182°C.;
2-(2-chlorobenzoyl)-HPI;
2 - (3 - chlorobenzoyl) - HPI; m.p. 181—182°C.;
2 - (4 - chlorobenzoyl) - HPI; m.p. 214—215°C.;
2-(2-bromobenozyl)-HPI;
2-(3-bromobenzoyl)-HPI;
2-(4-bromobenzoyl)-HYI;
2-(2-iodobenzoyl)-HPI;
2-(3-iodobenzoyl)-HPI;
2-(4-iodobenzoyl)-HPI;
2-(2,3-difluorobenzoyl)-HPI;
2-(2,4-difluorobenzoyl)-HPI;
2-(2,5-difluorobenzoyl)-HPI;
2-(2,6-difluorobenzoyl)-HPI;
2-(3,4-difluorobenzoyl)-HPI;

2-(3,5-difluorobenzoyl)-HPI;
2-(3,4-dichlorobenzoyl)-HPI;
2 - (3,5 - dichlorobenzoyl) - HPI; m.p. 165—166°C.;
2-(3,4-dibromobenzoyl)-HPI;
2-(3,5-dibromobenzoyl)-HPI;
2-(3,4,5-trifluorobenzoyl)-HPI;
2 - (2,3,4,5,6 - pentafluorobenzoyl) - HPI; m.p. 156°C.;
2-(2-hydroxybenzoyl)-HPI;
2-(3,hydroxybenzoyl)-HPI; m.p. 153°C.;
2 - (4 - hydroxybenzoyl) - HPI; m.p. 243—245°C.;
2-(3,4-dihydroxybenzoyl)-HPI;
2 - (3,5 - dihydroxybenzoyl) - HPI; m.p. 250—254°C. (decomposition)
2-(3,4,5-trihydroxybenzoyl)-HPI;
2-(3-methoxybenzoyl)-HPI;
2 - (4 - methoxybenzoyl) - HPI; m.p. 204—205°C.;
2 - (3 - acetoxybenzoyl) - HPI;
2 - (4 - acetoxybenzoyl) - HPI;
2-(3-trifluoroacetoxybenzoyl)-HPI;
2-(4-trifluoroacetoxybenzoyl)-HPI;
2-(3,4-dimethoxybenzoyl)-HPI;
2-(3,5-dimethoxybenzoyl)-HPI;
2-(3,4,5-trimethoxybenzoyl)-HPI;
2-(4-phenoxybenzoyl)-HPI;
2-(2-dimethylaminobenzoyl)-HPI;
2-(3-dimethylaminobenzoyl)-HPI;
2 - (4 - dimethylaminobenzoyl) - HPI; m.p. 225—226°C.
2-(2-diethylaminobenzoyl)-HPI;
2-(3-diethylaminobenzoyl)-HPI;
2-(4-diethylaminobenzoyl)-HPI;
2-(4-methylethylaminobenzoyl)-HPI;
2 - [3,4 - bis - (dimethylamino) - benzoyl]-HPI;
2 - [3,5 - bis - (dimethylamino) - benzoyl]-HPI;
2-(2-formamidobenzoyl)-HPI;
2-(3-formamidobenzoyl)-HPI; m.p. 176°C.
2 - (4 - formamidobenzoyl)-HPI; m.p. 207—208°C.;
2-(2-acetamidobenzoyl)-HPI;
2-(3-acetamidobenzoyl)-HPI;
2 - (4 - acetamidobenzoyl) - HPI; m.p. 247—248°C.;
2-(2-propionamidobenzoyl)-HPI;
2-(3-propionamidobenzoyl)-HPI;
2-(4-propionamidobenzoyl)-HPI;
2-(3-*n*-butyramidobenzoyl)-HPI;
2-(4-*n*-butyramidobenzoyl)-HPI;
2-[3,4-bis-(formamido)-benzoyl]-HPI;
2-[3,5-bis-(formamido)-benzoyl]-HPI;
2-(3-isobutyramidobenzoyl)-HPI;
2-(4-isobutyramidobenzoyl)-HPI;
2-(2-pentanoylaminobenzoyl)-HPI;
2-(3-pentanoylaminobenzoyl)-HPI;
2-(4-pentanoylaminobenzoyl)-HPI;
2-(2-hexanonylaminobenzoyl)-HPI;
2-(3-hexanoylaminobenzoyl)-HPI;
2-(4-hexanoylaminobenzoyl)-HPI;
2-(2-octanoylaminobenzoyl)-HPI;
2-(3-octanoylaminobenzoyl)-HPI;
2-(4-octanoylaminobenzoyl)-HPI;
2-(2-oleoylaminobenzoyl)-HPI;
2-(3-oleoylaminobenzoyl)-HPI;
2-(4-oleoylaminobenzoyl)-HPI;
2-(2-methylthiobenzoyl)-HPI;
2-(3-methylthiobenzoyl)-HPI;
2-(4-methylthiobenzoyl)-HPI; m.p. 195°C.;
2-(3-ethylthiobenzoyl)-HPI;
2-(4-ethylthiobenzoyl)-HPI;
2-[3,4-bis-(methylthio)-benzoyl]-HPI;
2-[3,5-bis-(methylthio)-benzoyl]-HPI;
2 - [3,4,5 - tris - (methylthio) - benzoyl]-HPI;
2-(4-phenylthiobenzoyl)-HPI;
2 - (2 - nitrobenzoyl) - HPI; m.p. 188—189°C.;
2-(3-nitrobenzoyl)-HPI; m.p. 172°C.;
2 - (3,4 - dinitrobenzoyl) - HPI; m.p. 219°C.;
2 - (3,5 - dinitrobenzoyl) - HPI; m.p. 251—252°C.;
2-(2-trifluoromethylbenzoyl)-HPI;
2 - (3 - trifluoromethylbenzoyl) - HPI; m.p. 148—149°C.;
2-(4-trifluoromethylbenzoyl)-HPI;
2-(2-cyanobenzoyl)-HPI;
2-(3-cyanobenzoyl)-HPI;
2-(4-cyanobenzoyl)-HPI; m.p. 214—215°C.:
2-(2-methoxycarbonylbenzoyl)-HPI;
2-(3-methoxycarbonylbenzoyl)-HPI;
2 - (4 - methoxycarbonylbenzoyl) - HPI; m.p. 178°C.;
2-(2-ethoxycarbonylbenzoyl)-HPI;
2-(3-ethoxycarbonylbenzoyl)-HPI;
2-(4-ethoxycarbonylbenzoyl)-HPI;
2 - [3,4 - bis - (methoxycarbonyl) - benzoyl]-HPI;
2 - [3,5 - bis - (methoxycarbonyl) - benzoyl]-HPI;
2-(2-azidobenzoyl)-HPI;
2-(3-azidobenzoyl)-HPI;
2-(2-methoxysulphonylbenzoyl)-HPI;
2-(3-methoxysulphonylbenzoyl)-HPI;
2-(4-methoxysulphonylbenzoyl)-HPI;
2-(2-ethoxysulphonylbenzoyl)-HPI;
2-(3-ethoxysulphonylbenzoyl)-HPI;
2-(4-ethoxysulphonylbenzoyl)-HPI;
2 - (2 - chloro - 4 - nitrobenzoyl) - HPI; m.p. 176—177°C.;
2 - (4 - chloro - 3 - nitrobenzoyl) - HPI; m.p. 192—194°C.;
2-(3-nitro-4-chlorobenzoyl)-HPI;
2 - (2 - hydroxy - 5 - chlorobenzoyl) - HPI; m.p. 180°C.;
2-naphthyl-1-carbonyl-HPI; m.p. 135°C.;
2-naphthyl-2-carbonyl-HPI; m.p. 178°C.;
2 - (1,2,3,4 - tetrahydronaphthyl - 1 - carbonyl)-HPI;
2 - (1,2,3,4 - tetrahydronaphthyl - 2 - carbonyl)-HPI;
2-(pyrryl-2-carbonyl-HPI; m.p. 174°C.;
2-(pyrryl-3-carbonyl)-HPI;
2 - (thienyl - 2 - carbonyl) - HPI; m.p. 132—133°C.;

2 - thienyl - 3 - carbonyl) - HPI; m.p. 142—143°C.;
2-(3-fluorothienyl-2-carbonyl)-HPI;
2-(4-fluorothienyl-2-carbonyl)-HPI;
2-(5-fluorothienyl-2-carbonyl)-HPI;
2-(3-nitrothienyl-2-carbonyl)-HPI;
2-(4-nitrothienyl-2-carbonyl)-HPI;
2 - (5 - nitrothienyl - 2 - carbonyl) - HPI; m.p. 172—173°C.
2 - (3 - dimethylaminothienyl - 2 - carbonyl)-HPI;
2 - (4 - dimethylaminothienyl - 2 - carbonyl)-HPI;
2-(3-formamidothienyl-2-carbonyl)-HPI;
2-(4-formamidothienyl-2-carbonyl)-HPI;
2-(3-methyl-thienyl-2-carbonyl)-HPI;
2-(4-methyl-thienyl-2-carbonyl)-HPI;
2 - (5 - methyl - thienyl - 2 - carbonyl)-HPI; m.p. 134—136°C.;
2-(2-methyl-thienyl-3-carbonyl)-HPI;
2-(4-methyl-thienyl-3-carbonyl)-HPI;
2-(5-methyl-thienyl-3-carbonyl)HPI;
2-(furyl-2-carbonyl)-HPI; m.p. 120°C.;
2-(furyl-3-carbonyl)-HPI;
2-(3-fluorofuryl-2-carbonyl)-HPI;
2-(4-fluorofuryl-2-carbonyl)-HPI;
2-(5-fluoromethyl-2-carbonyl)-HPI;
2-(5-chlorofuroyl-2-carbonyl)-HPI;
2 - (5 - bromofuryl - 2 - carbonyl) - HPI; m.p. 209°C.;
2 - (5 - nitrofuryl - 2 - carbonyl) - HPI; m.p. 182°C.;
2-(indolyl-2-carbonyl)-HPI;
2-(indolyl-3-carbonyl)-HPI;
2-(indolyl-4-carbonyl)-HPI;
2-(indolyl-5-carbonyl)-HPI; m.p. 235°C.;
2-(indolyl-6-carbonyl)-HPI;
2-(indolyl-7-carbonyl)-HPI;
2-(pyrazolyl-3-carbonyl)-HPI;
2-(pyrazolyl-4-carbonyl)-HPI;
2 - (5 - methyl - pyrazolyl - 3 - carbonyl)-HPI; m.p. 201°C.;
2 - (4 - methyl - pyrazolyl - 3 - carbonyl)-HPI;
2 - (4 - methyl - imidazolyl - 2 - carbonyl)-HPI;
2-(5-methyl-imidazolyl-2-carbonyl)-HPI;
2-(2-methyl-imidazolyl-4-carbonyl)-HPI;
2-(5-methyl-imidazolyl-4-carbonyl)-HPI;
2-(imidazolyl-2-carbonyl)-HPI;
2-(imidazolyl-4-carbonyl)-HPI;
2-(thiazolyl-2-carbonyl)-HPI;
2 - (4 - methyl - thiazolyl - 2 - carbonyl)-HPI;
2 - (5 - methyl - thiazolyl - 2 - carbonyl)-HPI;
2 - (thiazolyl - 4 - carbonyl) - HPI; m.p. 154°C.
2-(2-methyl-thiazolyl-4-carbonyl)-HPI;
2-(5-methyl-thiazolyl-4-carbonyl)-HPI;
2-(thiazolyl-5-carbonyl)-HPI;
2-(2-methyl-thiazolyl-5-carbonyl)-HPI;
2-(4-methyl-thiazolyl-5-carbonyl)-HPI;
2-(5-nitrothiazolyl-2-carbonyl)-HPI;
2 - (2,4 - dimethyl - thiazolyl - 5 - carbonyl)-HPI; m.p. 162—163°C.;
2-(benzthiazolyl-2-carbonyl)-HPI;
2-(benzthiazolyl-4-carbonyl)-HPI;
2-(benzthiazolyl-5-carbonyl)-HPI;
2-(isothiazolyl-3-carbonyl)-HPI;
2 - (4 - methyl - isothiazolyl - 3 - carbonyl)-HPI;
2 - (5 - methyl - isothiazolyl - 3 - carbonyl)-HPI;
2-(isothiazolyl-4-carbonyl)-HPI;
2 - (3 - methyl - isothiazolyl - 4 - carbonyl)-HPI;
2 - (5 - methyl - isothiazolyl - 4 - carbonyl)-HPI;
2-(isothiazolyl-5-carbonyl)-HPI;
2 - (3 - methyl - isothiazolyl - 5 - carbonyl)-HPI;
2 - (4 - methyl - isothiazolyl - 5 - carbonyl)-HPI;
2-(oxazolyl-2-carbonyl)-HPI;
2-(4-methyl-oxazolyl-2-carbonyl)-HPI;
2-(5-methyl-oxazolyl-2-carbonyl)-HPI;
2-(oxazolyl-4-carbonyl)-HPI;
2-(2-methyl-oxazolyl-4-carbonyl)-HPI;
2-(5-methyl-oxazolyl-4-carbonyl)-HPI;
2-(oxazolyl-5-carbonyl)-HPI;
2-(2-methyl-oxazolyl-5-carbonyl)-HPI;
2-(4-methyl-oxazolyl-5-carbonyl)-HPI;
2-(isoxazolyl-3-carbonyl)-HPI;
2-(isoxazolyl-4-carbonyl)-HPI;
2-(3-methyl-isoxazolyl-4-carbonyl)-HPI;
2-(5-methyl-isoxazolyl-4-carbonyl)-HPI;
2-(isoxazolyl-5-carbonyl)-HPI;
2-(3-methyl-isoxazolyl-5-carbonyl)-HPI;
2-(4-methyl-isoxazolyl-5-carbonyl)-HPI;
2 - (5 - methyl - isoxazolyl - 3 - carbonyl)-HPI; m.p. 173—174°C.;
2-(4-methyl-isoxazolyl-3-carbonyl)-HPI;
2-picolinoyl-HPI hydrobromide; m.p. 163°C.;
2-(3-fluoropicolinoyl)-HPI;
2-(4-fluoropicolinoyl)-HPI;
2-(5-fluoropicolinoyl)-HPI;
2-(6-fluoropicolinoyl)-HPI;
2-(3-diethylaminopicolinoyl)-HPI;
2-(4-diethylaminopicolinoyl)-HPI;
2-(5-diethylaminopicolinoyl)-HPI;
2-(6-diethylaminopicolinoyl)-HPI;
2-(3-formamidopicolinoyl)-HPI;
2-(4-formamidopicolinoyl)-HPI;
2-(5-formamidopicolinoyl)-HPI;
2-(6-formamidopicolinoyl)-HPI;
2-nicotinoyl-HPI; m.p. 172°C.;
2-(2-fluoronicotinoyl)-HPI;
2-(4-fluoronicotinoyl)-HPI;
2-(5-fluoronicotinoyl)-HPI;
2-(6-fluoronicotinoyl)-HPI;
2-(2-chloronicotinoyl)-HPI;
2-(4-chloronicotinoyl)-HPI; m.p. 158°C.;
2-(5-chloronicotinoyl)-HPI;
2-(6-chloronicotinoyl)-HPI;
2-(2-hydroxynicotinoyl)-HPI;
2-(4-hydroxynicotinoyl)-HPI;
2-(5-hydroxynicotinoyl)-HPI;
2-(6-hydroxynicotinoyl)-HPI;
2-(2-dimethylaminnicotinoyl)-HPI;

2-(4-dimethylaminonicotinoyl)-HPI;
2-(5-dimethylaminonicotinoyl)-HPI;
2-(6-dimethylaminonicotinoyl)-HPI;
2-(2-formamidonicotinoyl)-HPI;
2-(4-formamidonicotinoyl)-HPI;
2-(5-formamidonicotinoyl)-HPI;
2-(6-formamidonicotinoyl)-HPI;
2-(2-acetamidonicotinoyl)-HPI;
2-(4-acetamidonicotinoyl)-HPI;
2-(5-acetamidonicotinoyl)-HPI;
2-(6-acetamidonicotinoyl)-HPI;
2-isonicotinoyl-HPI; m.p. 140—141°C.;
2 - (2,6 - dichloroisonicotinoyl) - HPI; m.p. 207—208°C.;
2 - (quinolyl - 2 - carbonyl) - HPI; m.p. 198—208°C.;
2-(quinolyl-3-carbonyl)-HPI;
2-(quinolyl-4-carbonyl)-HPI;
2-(quinolyl-5-carbonyl)-HPI;
2-(quinolyl-6-carbonyl)-HPI;
2-(quinolyl-7-carbonyl)-HPI;
2-(quinolyl-8-carbonyl)-HPI;
2 - (isoquinolyl - 1 - carbonyl) - HPI; m.p. 157°C.;
2-(isoquinolyl-3-carbonyl)-HPI;
2-(pyridazinyl-3-carbonyl)-HPI;
2-(pyridazinyl-4-carbonyl)-HPI;
2-(pyrimidinyl-2-carbonyl)-HPI;
2-(pyrimidinyl-4-carbonyl)-HPI;
2-(pyrimidinyl-5-carbonyl)-HPI;
2 - (pyrazinyl - 2 - carbonyl) - HPI; m.p 153—154°C.;
2-(purinyl-2-carbonyl)-HPI;
2-(purinyl-6-carbonyl)-HPI;
2-(purinyl-8-carbonyl)-HPI;
2 - nalidixinyl - HPI (i.e. 2 - (1 - ethyl - 7 - methyl - 1,8 - naphthyridin - 4 - on - 3-carbonyl)-HPI);
2 - (1,4 - dioxanyl - 2 - carbonyl) - HPI;
2 - (4 - methyl - piperazinyl - 1 - carbonyl)-HPI; hydrochloride; m.p. 290°C.;
2-(dihydrofuryl-2-carbonyl)-HPI;
2-(tetrahydrofuryl-2-carbonyl)-HPI;
2-(tetrahydrofuryl-3-carbonyl)-HPI;
2 - (1 - methyl - 1,2,5,6 - tetrahydropyridyl-3 - carbonyl) - HPI hydrochloride; m.p. 211°C.;
2 - (1 -methyl - 1,4,5,6 - tetrahydropyridyl-3-carbonyl)-HPI;
2-(1-methylpiperidyl-2-carbonyl)-HPI;
2-(1-methylpiperidyl-3-carbonyl)-HPI;
2-(1-methylpiperidyl-4-carbonyl)-HPI;
2-(1-ethylpiperidyl-2-carbonyl)-HPI;
2-(1-ethylpiperidyl-3-carbonyl)-HPI;
2-(1-ethylpiperidyl-4-carbonyl)-HPI;
2-(1-benzylpiperidyl-2-carbonyl)-HPI;
2-(1-benzylpiperidyl-3-carbonyl)-HPI;
2-(1-benzoyl-piperidyl-4-carbonyl)-HPI;
2-(1-formylpiperidyl-3-carbonyl)-HPI;
2 - (1 - formylpiperidyl - 4 - carbonyl) - HPI; m.p. 160°C.;
2-(1-acetylpiperidyl-2-carbonyl)-HPI;
2-(1-acetylpiperidyl-3-carbonyl)-HPI;
2-(1-acetylypiperidyl-4-carbonyl)-HPI;
2-(1-hexanoylpiperidyl-2-carbonyl)-HPI;
2-(1-hexanoylpiperidyl-3-carbonyl)-HPI;
2 - (1 - hexanoylpiperidyl - 4 - carbonyl)-HPI;
2 - (1 - octanoylpiperidyl - 2 - carbonyl)-HPI;
2 - (1 - octanoylpiperidyl - 3 - carbonyl)-HPI;
2 - (1 - octanoylpiperidyl - 4 - carbonyl)-HPI;
2-(1-oleoylpiperidyl-2-carbonyl)-HPI;
2-(1-oleoylpiperidyl-3-carbonyl)-HPI;
2-(1-oleoylpiperidyl-4-carbonyl)-HPI;
2 - [1 - (methoxyacetyl) - piperidyl - 2-carbonyl]-HPI;
2 - [1 - (methoxyacetyl) - piperidyl - 3-carbonyl]-HPI;
2 - [1 - (methoxyacetyl) - piperidyl - 4-carbonyl]-HPI;
2 - [1 - (ethoxyacetyl) - piperidyl - 2-carbonyl]-HPI;
2 - [1 - (ethoxyacetyl) - piperidyl - 3-carbonyl]-HPI;
2 - [1 - (ethoxyacetyl) - piperidyl - 4-carbonyl]-HPI;
2-(tetrahydropyranyl-2-carbonyl)-HPI;
2-(tetrahydropyranyl-3-carbonyl)-HPI;
2 - (tetrahydropyranyl - 4 - carbonyl) - HPI; m.p. 172°C.;
2 - (chromon - 2 - carbonyl) - HPI; m.p. 155—156°C.;
2 - (tetrahydrothiopyranyl - 2 - carbonyl)-HPI;
2 - (tetrahydrothiopyranyl - 3 - carbonyl)-HPI;
2 - (tetrahydrothiopyranyl - 4 - carbonyl)-HPI; m.p. 168°C.;
2-(1,2,3-thiadiazolyl-4-carbonyl)-HPI;
2 - (2,1,3 - benzothiadiazolyl - 5 - carbonyl)-HPI; m.p. 144°C.;

Example 2.

1 ml. phosphorus trichloride is added dropwise, at 140°C. (bath temperature) to a solution of 6.1 g. HPI and 5.5 g. 5-chlorosalicylic acid in 50 ml. chlorobenzene. The reaction mixture is boiled for one hour, evaporated and the residue chromatographed over silica gel with chloroform as eluant. 2 - (5 - Chloro - 2-hydroxybenzoyl) - HPI is obtained which, after recrystallisation from isopropanol, melts at 180°C.

Example 3.

10.1 g. HPI, 6.75 g. isonicotinic acid and 5.5 g. silicon tetrachloride are boiled for one hour in 150 ml. pyridine. The reaction mixture is poured on to ice, extracted with chloroform and washed with water. After drying the chloroform solution over anhydrous sodium sulphate and evaporating, 2 - (isonicotinoyl)-HPI is obtained which, after recrystallising from ethanol, melts at 140—141°C.

Example 4.

6.1 g. HPI and 1.4 g. formic acid are heated

for 5 hours in 100 ml. toluene, the resulting water being distilled off. After cooling, there is obtained 2-formyl-HPI which, after recrystallisation from ethanol, melts at 206°C.

Example 5.

4.04 g .HPI and 3.4 g. cyclohexane-1,2-*trans*-dicarboxylic anhydride are each dissolved in 25 ml. methylene chloride at 20°C. and then mixed together. The reaction mixture is left to stand and then evaporated to give 2-(2 - *trans* - carboxy - cyclohexylcarbonyl)-HPI which, after recrystallisation from ethyl acetate/petroleum ether, melts at 208—210°C.

Analogously, but after 6 hours boiling in dioxan, with cyclohexane - 1,2 - *cis* - dicarboxylic anhydride, there is obtained 2 - (2-*cis* - carboxy - cyclohexylcarbonyl) - HPI; m.p. 194—196°C.

Analogously, with cyclobutane - 1,2 - dicarboxylic anhydride, cyclopentane - 1,2 - dicarboxylic anhydride, cycloheptane - 1,2 - dicarboxylic anhydride, phthalic anhydride and succinic anhydride, there are obtained:

2 - (2 - *trans* - carboxycyclopentyl - carbonyl)-HPI;
2 - (2 - *trans* - carboxycycloheptyl - carbonyl)-HPI;
2 - (2 - *cis* - carboxycyclobutyl - carbonyl)-HPI;
2 - (2 - *cis* - carboxycyclopentyl - carbonyl)-HPI;
2 - (2 - *cis* - carboxycycloheptyl - carbonyl)-HPI;
2-(2-carboxybenzoyl)-HPI;
2-(3-carboxypropionyl)-HPI.

Example 6.

Analogously to Example 1, from the (+)- and (−)- antipodes of HPI and the corresponding acid chlorides, there are obtained:

(+)-2-acetyl-HPI; m.p. 175—176°C.;
(−)-2-acetyl-HPI; m.p. 177—178°C.;
(+)-2-propionyl-HPI;
(−)-2-propionyl-HPI;
(+)-2-isobutyryl-HPI;
(−)-2-isobutyryl-HPI;
(+)-2-trimethylacetyl-HPI;
(−)-2-trimethylacetyl-HPI;
(+)-2-(3,3-dimethyl-*n*-butyryl)-HPI;
(−)-2-(3,3-dimethyl-*n*-butyryl)-HPI;
(+)-2-heptanoyl-HPI;
(−)-2-heptanoyl-HPI;
(+)-2-(thienyl-2-mercaptoacetyl)-HPI;
(−)-2-(thienyl-2-mercaptoacetyl)-HPI;
(+)-2-cyclopropyl-carbonyl-HPI;
(−)-2-cyclopropyl-carbonyl-HPI;
(+)-2-cyclobutyl-carbonyl-HPI;
(−)-2-cyclobutyl-carbonyl-HPI;
(+)-2-cyclopentyl-carbonyl-HPI;
(−)-2-cyclopentyl-carbonyl-HPI;
(+) - 2 - cyclohexyl - carbonyl - HPI; m.p. 108—110°C.; $[\alpha] = +145.2°$;
(−) - 2 - cyclohexyl - carbonyl - HPI; m.p. 107—108°C.; $[\alpha] = -146.9°$;
(+) - 2 - (4 - formamidocyclohexyl - carbonyl)-HPI;
(−) - 2 - (4 - formamidocyclohexyl - carbonyl)-HPI;
(+)-2-cycloheptyl-carbonyl-HPI;
(−)-2-cycloheptyl-carbonyl-HPI;
(+)-2-cyclooctyl-carbonyl-HPI;
(−)-2-cyclooctyl-carbonyl-HPI;
(+) - 2 - (4 - methylbenzoyl) - HPI; m.p. 180—181°C.; $[\alpha] = +29.2°$;
(−) - 2 - (4 - methylbenzoyl) - HPI; m.p. 181—182°C.; $[\alpha] = -28.5°$;
(+) - 2 -(4 - *tert.* - butylbenzoyl) - HPI; m.p. 181—182°C.; $[\alpha] = +21.5°$;
(−) - 2 - (4 - *tert.* - butylbenzoyl) - HPI; m.p. 168—169°C.; $[\alpha] = -20.5°$;
(+) - 2 - (2 - fluorobenzoyl) - HPI; m.p. 155—156°C.; $[\alpha] = +49.1°$.;
(−) - 2 - (2 - fluorobenzoyl) - HPI; m.p. 159—161°C.; $[\alpha] - 49.9°$;
(+) - 2 - (3 - fluorobenzoyl) - HPI; m.p. 156—158°C.; (sinters 148°C.) $[\alpha] = +40.2°$;
(−) - 2 - (3 - fluorobenzoyl) - HPI; m.p. 156°C.; $[\alpha] = -41.6°$;
(+) - 2 - (4 - fluorobenzoyl) - HPI; m.p. 200—201°C.; $[\alpha] = +33.5°$;
(−) - 2 - (4 - fluorobenzoyl) - HPI; m.p. 202—203°C.; $[\alpha] = -32.6°$;
(+)-2-(3-chlorobenzoyl)-HPI;
(−)-2-(3-chlorobenzoyl)-HPI;
(+) - 2 - (4 - chlorobenzoyl) - HPI; m.p. 231—232°C.; $[\alpha] = +20.4°$;
(−) - 2 -(4 - chlorobenzoyl) - HPI; m.p. 233—234°C.; $[\alpha] = -20.7°$;
(+)-2-(3-hydroxybenzoyl)-HPI;
(−)-2-(3-hydroxybenzoyl)-HPI;
(+)-2-(4-hydroxybenzoyl)-HPI;
(−)-2-(4-hydroxybenzoyl)-HPI;
(+) - 2 - (4 - methoxybenzoyl)- HPI; m.p. 215°C.; $[\alpha] = +19.8°$;
(−) - 2 - (4 - methoxybenzoyl) - HPI; m.p. 216°C.; $[\alpha] - 18.7°$;
(+)-2-(3-dimethylaminobenzoyl)-HPI;
(−)-2-(3-dimethylaminobenzoyl)-HPI;
(+)-2-(4-dimethylaminobenzoyl)-HPI;
(−)-2-(4-dimethylaminobenzoyl)-HPI;
(+)-2-(4-diethylaminobenzoyl)-HPI;
(−)-2-(4-diethylaminobenzoyl)-HPI;
(+)-2-(2-formamidobenzoyl)-HPI;
(−)-2-(2-formamidobenzoyl)-HPI;
(+)-2-(3-formamidobenzoyl)-HPI;
(−)-2-(3-formamidobenzoyl)-HPI;
(+) - 2 - (4 - formamidobenzoyl) - HPI; m.p. 193°C.; $[\alpha] = +8.6°$;
(−) - 2 - (4 - formamidobenzoyl) - HPI; m.p. 193°C.; $[\alpha] -8.4°$;
(+)-2-(2-acetamidobenzoyl)-HPI;
(−)-2-(2-acetamidobenzoyl)-HPI;
(+)-2-(3-acetamidobenzoyl)-HPI;
(−)-2-(3-acetamidobenzoyl)-HPI;
(+)-2-(4-acetamidobenzoyl)-HPI;
(−)-2-(4-acetamidobenzoyl)-HPI;

(+)-2-(2-nitorbenzoyl)-HPI;
(−)-2-(2-nitrobenzoyl)-HPI;
(+) - 2 - (3 - nitrobenzoyl) - HPI; m.p. 139°C.; [α] = +2.9° (from the (−)-base);
(−) - 2 - (3 - nitrobenzoyl) - HPI; m.p. 139°C.; [α] = −2.9° (from the (+)-base);
(+) - 2 - (4 - nitrobenzoyl) - HPI; m.p. 223—224°C.; [α] = +18.5°;
(−) - 2 - (4 - nitrobenzoyl) - HPI; m.p. 223—224°C.; [α] = −21.4°;
(+)-2-(thienyl-2-carbonyl)-HPI;
(−)-2-(thienyl-2-carbonyl)-HPI;
(+)-2-(thienyl-3-carbonyl)-HPI;
(−)-2-(thienyl-3-carbonyl)-HPI;
(+)-2-(5-methyl-thienyl-2-carbonyl)-HPI;
(−)-2-(5-methyl-thienyl-2-carbonyl)-HPI;
(+)-2-(furyl-2-carbonyl-HPI;
(−)-2-(furyl-2-carbonyl)-HPI;
(+)-2-picolinoyl-HPI;
(−)-2-picolinoyl-HPI;
(+) - 2 - nicotinoyl - HPI; m.p. 148°C.; [α] = +25.5°;
(−) - 2 - nicotinoyl - HPI; m.p. 156°C.; [α] = −28.4°;
(+)-2-isonicotinoyl-HPI;
(−)-2-isonicotinoyl-HPI;
(+)-2-nicotinoyl-HPI-1'-N-oxide;
(−)-2-nicotinoyl-HPI-1'-N-oxide;
(+) - 2 - (tetrahydropyranyl - 4 - carbonyl)-HPI;
(−) - 2 - (tetrahydropyranyl - 4 - carbonyl)-HPI;
(+) - 2 - (tetrahydrothiopyranyl - 4 - carbonyl)-HPI;
(−) - 2 - (tetrahydrothiopyranyl - 4 - carbonyl)-HPI;
(+) - 2 - (N - formyl - piperidyl - 4 - carbonyl)-HPI;
(−) - 2 - (N - formyl - piperidyl - 4 - carbonyl)-HPI.

Example 7.

3.8 g. 3 - trifluoromethyl - benzoyl fluoride in 50 ml. chloroform are added dropwise to 4.04 g. HPI and 2.8 ml. triethylamine in 50 ml. chloroform. The reaction mixture is kept for one hour at 20°C., shaken out with dilute hydrochloric acid and water, dried over anhydrous sodium sulphate and evaporated to give 2 - (3 - trifluoromethylbenzoyl) - HPI which, after recrystallisation from ethanol, melts at 148—149°C.

Example 8.

Analogously to Example 1, from HPI and *p*-nitrobenzoyl bromide in chloroform in the presence of triethylamine, there is obtained, after 2 hours, 2 - (4 - nitrobenzoyl) - HPI; m.p. 212—213°C.

Example 9.

Analogously to Example 1, from HPI and *p*-nitrobenzoyl iodide in chloroform in the presence of triethylamine, there is obtained, at 40°C. after 2 hours, 2 - (4 - nitrobenzoyl)-HPI; m.p. 212—213°C.

Example 10.

To 8.5 g. 3 - (2 - chloroacetyl - 1,2,3,4-tetrahydroisoquinolinyl - 1 - methyl) - 4-fluorobenzamide (obtainable by hydrogenation of 1 - cyano - 2 - (4 - fluorobenzoyl) - 1,2-dihydroisoquinoline on Raney nickel at 100°C. and 250 ats. pressure and reaction of the N - (1,2,3,4 - tetrahydroisoquinolinyl - 1-methyl) - 4 - fluorobenzamide obtained with chloroacetyl chloride in chloroform in the presence of triethylamine) in 300 ml. absolute tetrahydrofuran, there are added dropwise, under nitrogen, at 20°C., 12 ml. 20% butyl lithium solution in hexane. The reaction mixture is stirred for 2 hours at 20°C. and boiled for a further 12 hours. After the addition of water, the solvent is removed and the residue is taken up in chloroform. The chloroform solution is shaken with water, dried and evaporated to give 2-(4-fluorobenzoyl)-HPI which, after recrystallisation from methanol, melts at 181—182°C.

Analogously, from 8.5 g. (+)-N-(2-chloroacetyl - 1,2,3,4 - tetrahydroisoquinolinyl - 1-methyl) - 4 - fluorobenzamide and butyl lithium, there is obtained (−) - 2 - (4-fluorobenzoyl)HPI; m.p. 202—203°C.; [α] = −32.6°.

Analogously, from N - (2 - bromoacetyl-1,2,3,4 - tetrahydroisoquinolinyl - 1 -methyl)-4 - methylbenzamide or from N - (2 - iodoacetyl - 1,2,3,4 - tetrahydroisoquinolinyl - 1-methyl) - 4 - methylbenzamide or from N-(2-*p* - toluenesulphonyloxyacetyl - 1,2,3,4 - tetrahydroisoquinolinyl - 1 -methyl) - 4 - methylbenzamide and butyl lithium, there is also obtained 2 - (4 - methylbenzoyl) - HPI; m.p. 183—184°C.

Analogously, from N - (2 - chloroacetyl-1,2,3,4 - tetrahydroisoquinolinyl - 1 -methyl)-cyclohexyl - carboxamide and butyl lithium, there is obtained 2 - cyclohexyl - carbonyl-HPI; m.p. 136—138°C.

Example 11.

15 g. nickel-aluminium alloy (1:1) are introduced in portions and with stirring into 200 ml. 20% sodium hydroxide solution within the sourse of 5 minutes and maintained for 45 minutes at 80°C. After leaving to settle, supernatant liquid is decanted off, the solid is washed 4 times with water and 1000 ml. 1% (−)-tartaric acid solution, which has been adjusted to pH 5 with 1N aqueous sodium hydroxide solution added thereto. With repeated shaking up, the mixture is heated for 90 minutes at 80°C., whereafter supernatant liquid is decanted off and the solid material is washed several times with water and methanol. The (−)-tartaric acid-Raney nickel catalyst thus obtained is added to a solution of 322

mg. 2 - (4 - fluorobenzoyl) - 4 - oxo - 2,3,6,7-tetrahydro - 4H - pyrazino - [2,1 - a] - isoquinoline (obtainable by the dehydrogenation of (±)- or (+) - 2 - (4 - fluorobenzoyl)-HPI with sulphur) in 40 ml. methanol, followed by hydrogenation at atmospheric pressure and ambient temperature. After filtering off the catalyst and evaporating the solvent, there is obtained (−) - 2 - (4 - fluorobenzoyl)-HPI in 23% optical purity; m.p. 190—193°C.; $[\alpha] = -7.5°$.

Analogously, from 2 - cyclohexyl - carbonyl-4 - oxo - 2,3,6,7, - tetrahydro - 4H - pyrazino-[2,1 - a]isoquinoline, there is obtained (−)-2 - cyclohexyl - carbonyl - HPI in 20% optical purity; m.p. 122—127°C.; $[\alpha] = -29.3°$.

Example 12.

322 mg. 2 - (4 - fluorobenzoyl) - 4 - oxo-2,3,6,7 - tetrahydro - 4H - pyrazino[2,1-a]-isoquinoline are hydrogenated analogously to Example 11 in 40 ml. methanol in the presence of 300 mg. Raney nickel to give racemic 2-(4-fluorobenzoyl)-HPI; m.p. 181—182°C.

Analogously, from 2 - cyclohexylcarbonyl-4 - oxo - 2,3,6,7 - tetrahydro - 4H - pyrazino-[2,1-a6isoquinoline, there is obtained 2-cyclohexylcarbonyl-HPI; m.p. 136—138°C.

Example 13.

A solution of 67.7 g. 2 - (4 - nitrobenzoyl)-HPI in 1500 ml. methanol are hydrogenated in the presence of 12 g. 5% palladium charcoal at 20°C. under atmospheric pressure. The catalyst is filtered off and the filtrate is evaporated. From the residue, there is obtained 2 - (4 - aminobenzoyl) - HPI which, after recrystallisation from ethanol, melts at 212—213°C.; hydrochloride: m.p. 165—166°C. (decomposition); sulphate: m.p. 234—235°C.; isothionate: m.p. 233—234°C.

The following compounds are obtained analogously by hydrogenation of the corresponding nitro compounds:

2-aminoacetyl-HPI;
2-(2-amino-propionyl)-HPI;
2-(3-aminopropionyl)-HPI;
2-(2-amino-*n*-butyryl)-HPI;
2-(4-amino-*n*-butyryl)-HPI;
2-(2-amino-*n*-valeryl)-HPI;
2-(5-amino-*n*-valeryl)-HPI;
2-(3-aminophenoxyacetyl)-HPI;
2-(4-aminophenoxyacety!)-HPI;
2-(2-aminocyclopropyl-carbonyl)-HPI;
2-(1-aminocyclobutyl-carbonyl)-HPI;
2-(2-aminocyclobutyl-carbonyl)-HPI;
2-(3-aminocyclobutyl-carbonyl)-HPI;
2-(1-aminocyclopentyl-carbonyl)-HPI;
2-(2-aminocyclopentyl-carbonyl)-HPI;
2-(3-aminocyclopentyl-carbonyl)-HPI;
2-(1-aminocyclohexyl-carbonyl)-HPI;
2-(2-amniocyclohexyl-carbonyl)-HPI;
2-(3-aminocyclohexyl-carbonyl)-HPI;
cis - 2 - (4 - aminocyclohexyl - carbonyl)-HPI; amorphous; IR 3500, 3300 and 1645 cm^{-1};
trans - 2 - (4 - aminocyclohexyl - carbonyl)-HPI; m.p. 284°C.;
2-(4-aminocycloheptyl-carbonyl)-HPI;
2 - (2 - aminobenzoyl) - HPI hydrobromide; m.p. 279—280°C.;
2 - (3 - aminobenzoyl) - HPI; m.p. 161—162°C.;
(+) - 2 - (3 - aminobenzoyl) - HPI; m.p. 164—165°C.; $[\alpha] = +35.9°$ (from the (−)-nitro antipode)
(−) - 2 - (3 - aminobenzoyl) - HPI; m.p. 164—165°C.; $[\alpha] = -36.5°$ (from the (+)-nitro antipode)
(+) - 2 - (4 - aminobenzoyl) - HPI; m.p. 231—232°C.; $[\alpha] = +23.1°$; hydrobromide: m.p. from 193°C. (decomposition); isethionate: m.p. 200—210°C.; $[\alpha] = +16.0°$;
(−) - 2 - (4 - aminobenzoyl) - HPI; m.p. 231—232°C.; $[\alpha] = -23.0°$; hydrobromide: m.p. from 205°C. (decomposition); isethionate: m.p. 200—210°C.; $[\alpha] = -16.3°$;
2 - (3,4 - diaminobenzoyl) - HPI; m.p. 143°C.;
2 - (3,5 - diaminobenzoyl) - HPI; m.p. 235—236°C.;
2 - (2 - chloro - 4 - amino - benzoyl) - HPI; m.p. 145°C.; hydrochloride: 181—182°C.;
2-(2-chloro-5-amino-benzoyl)-HPI;
2-(3-chloro-4-amino-benzoyl)-HPI;
2-(3-chloro-5-amino-benzoyl)-HPI;
2-(2-amino-3-chlorobenzoyl)HPI;
2-(2-amino-4-chlorobenzoyl)-HPI;
2-(2-amino-5-chlorobenzoyl)-HPI;
2 - (3 - amino - 4 - chlorobenzoyl) - HPI; hydrobromide m.p. 208—210°C.;
2-(3-amino-thienyl-2-carbonyl)-HPI;
2-(4-amino-thienyl-2-carbonyl)-HPI;
2 - (4 - amino - tetrahydrothiopyranyl - 4-carbonyl) - HPI; m.p. 157—158°C.;
2-(4-aminonicotinoyl)-HPI;
2-(5-aminonicotinoyl)-HPI.

Example 14.

2.4 g. acetyl chloride in 100 ml. chloroform are added to 9.6 g. 2-(4-aminobenzoyl)-HPI and 3.1 g. triethylamine in 300 ml. chloroform and the reaction mixture left to stand for 2 hours at ambient temperature. A further 2.4 g. acetyl chloride and 3.1 g. triethylamine are then added thereto and the reaction mixture boiled for 3 hours, whereafter it is washed with dilute hydrochloric acid and water. After evaporation of the solvent, the residue is recrystallised from acetone to give 2-(4-acetyl-aminobenzoyl)-HPI; m.p. 247—248°C.

The following compounds are obtained analogously with the use of appropriate acylating agents:

2-acetamidoacetyl-HPI;
2 - (1 - acetamidocyclohexyl - carbonyl)-HPI;
2 - (2 - acetamidocyclohexyl - carbonyl)-HPI;
2 - (3 - acetamidocyclohexyl - carbonyl)-HPI;
2 - (4 - acetamidocyclohexyl - carbonyl)-HPI;
2 - (4 - propionamidocyclohexyl - carbonyl)-HPI;
2 - (4 - pentanoylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - hexanoylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - octanoylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - oleoylaminocyclohexyl - carbonyl)-HPI;
2 - (2 - sulphaminoacetyl) - HPI (with chlorosulphonic acid);
2 - (4 - sulphaminocyclohexyl - carbonyl) HPI;
2-(3-sulphaminobenzoyl)-HPI;
2-(4-sulphonaminobenzoyl)-HPI;
2 - (1 - sulpho - piperidyl - 4 - carbonyl)-HPI.

Example 15.

A solution of 3.5 g. 2 - [4 - methyl - nitrosamino - benzoyl] - HPI (prepared by nitrosating 2 - (4 - methylaminobenzoyl) - HPI) in 5 ml. glacial acetic acid is slowly added, with vigorous stirring, to 2.7 g. zinc dust in 5 ml. water. The reaction mixture is stirred for 2 hours at 20°C., then heated to 80°C. and filtered hot. The residue is washed with 5% hydrochloric acid and the combined filtrates are rendered alkaline and extracted with chloroform. The extract is washed neutral with water and evaporated to give 2 - [4 - (1-methylhydrazino) - benzoyl] - HPI.

The following compounds are prepared analogously:

2 - [2 - (1 - methylhydrazino) - benzoyl]-HPI;
2 - [3 - (1 - methylhydrazino) - benzoyl]-HPI;
2 - [4 - (1 - ethylhydrazino) - benzoyl]-HPI.

Example 16.

8 ml. of 30% hydrogen peroxide in 0.8 ml. 6N aqueous sodium hydroxide solution are added to 5 g. 2 - (4 - cyanobenzoyl) - HPI in 20 ml. ethanol. Heating occurs with the evolution of oxygen. The temperature is maintained for 1 hour between 40 and 50°C., whereafter the reaction mixture is cooled and mixed with 5 ml. water. 2 - (4 - Carboxamidobenzoyl)-HPI is obtained.

2 - (3 - Carboxamidobenzoyl) - HPI is prepared analogously from 2 - (3 - cyanobenzoyl)-HPI.

Example 17.

A mixture of 8 g. 2 - (4 - methoxycarbonylbenzoyl) - HPI in 500 ml. 10% aqueous sodium hydroxide solution is stirred for 12 hours at 20°C. Insoluble material is filtered off and the filtrate is acidified with hydrochloric acid and extracted with chloroform. The residue is purified chromatographically on silica gel (eluent: chloroform/methanol). 2-(4-Carboxybenzoyl)-HPI is obtained; m.p. 251°C.

The following compounds are obtained analogously by alkaline saponification:

2-(2-carboxycyclopropyl-carbonyl)-HPI;
2-(2-carboxycyclobutyl-carbonyl)-HPI;
2-(3-carboxycyclobutyl-carbonyl)-HPI;
2-(2-carboxycyclopentyl-carbonyl)-HPI;
2-(3-carboxycyclopentyl-carbonyl)-HPI;
trans - 2 - (2 - carboxycyclohexyl - carbonyl)-HPI; m.p. 208—210°C.;
cis - 2 -(2 - carboxycyclohexyl - carbonyl-HPI; m.p. 194—196°C.;
2-(3-carboxycyclohexyl-carbonyl)-HPI;
2-(4-carboxycyclohexyl-carbonyl)-HPI;
2-(2-carboxybenzoyl)-HPI;
2-(3-carboxybenzoyl)-HPI;
2-(3,4-dicarboxy-benzoyl)-HPI;
2-(3,5-dicarboxy-benzoyl)-HPI.

Example 18.

A solution of 32 g. 2 - (4 - hydroxybenzoyl-HPI in 150 ml. methanol/water (10:1) is mixed with an excess of ethereal diazomethane solution until a pale yellow coloration remains. The reaction mixture is evaporated and the residue is taken up in ether, washed with dilute aqueous sodium hydroxide solution and water, dried over anhydrous sodium sulphate and evaporated to give 2 - (4 - methoxybenzoyl) - HPI; m.p. 204—205°C.

Example 19.

7.5 g. boron tribromide are added dropwise to 5.4 g. 2 - (4 - methoxybenzoyl) - HPI in 100 ml. methylene chloride at −5 to −10°C. The reaction mixture is stirred for one hour at 20°C. and then poured on to ice. The organic phase is separated off and the aqueous phase is shaken out several times with methylene chloride. The combined organic phases are dried over anhydrous sodium sulphate and subsequently evaporated. From the residue, there is obtained 2 - (4 - hydroxybenzoyl) - HPI which, after recrystallisation from ethanol, melts at 243—245°C.

Example 20.

3.22 g. 2 - (4 - hydroxybenzoyl) - HPI, 1.02 g. acetic anhydride and 100 ml. pyridine are boiled for 3 hours, subsequently poured on to ice, extracted with ether, washed with water and dried over anhydrous sodium sulphate to give 2 - (4 - acetoxybenzoyl) - HPI.

Example 21.

A mixture of 4.8 g. 2 - (4 - aminobenzoyl)-HPI and 1.5 g. 33% formaldehyde solution in 200 ml. methanol is hydrogenated in the presence of 5% palladium charcoal. Subsequently, the catalyst is filtered off, the solvent is evaporated off and the residue is purified chromatographically on silica gel (eluent: chloroform). 2 - (4 - Methylaminobenzoyl)-HPI is obtained; m.p. 220°C.

Example 22.

Analogously to Example 21, from 4.8 g. 2 - (4 - aminobenzoyl) - HPI and 4 g. 33% formaldehyde solution, there is obtained 2-(4-dimethylaminobenzoyl) - HPI; m.p. 225—226°C.

Example 23.

Within the course of 2 hours and with the exclusion of moisture, 3.2 g. 2 - (4 - aminobenzoyl) - HPI in 100 ml. dioxan are mixed with 2.5 g. dimethyl sulphate and subsequently stirred for 15 hours at 100°C. After cooling, 1.4 g. potassium hydroxide in 5 ml. water are added thereto, followed by extraction with chloroform. After evaporation there is obtained 2 - (4 - dimethylaminobenzoyl)- HPI; m.p. 225—226°C .

Example 24.

10.4 g. 2 - (4 - trifluoroacetamidobenzoyl)-HPI (obtainable from 2 - (4 - aminobenzoyl)-HPI by reaction with trifluoroacetic anhydride/triethylamine) are heated almost to the boil with 34.2 g. methyl iodide in 300 ml. dry acetone. 13.4 g. pulverised potassium hydroxide are added thereto and the reaction mixture is boiled for 5 minutes, whereafter it is evaporated to dryness, the residue mixed with water and stirred for 2 hours at 20°C. Thereupon, it is extracted with chloroform, washed with water and evaporated to give 2 - (4 - methylaminobenzoyl) - HPI; m.p. 220°C.

If the methyl iodide is not removed before the hydrolysis, then 2 - (4 - dimethylaminobenzoyl)-HPI is obtained; m.p. 225—226°C.

Example 25.

Analogously to Example 19, from 2-(4-methylmercaptobenzoyl)-HPI and boron tribromide, there is obtained 2-(4-mercaptobenzoyl)-HPI.

2 - (2 - Mecaptobenzoyl) - HPI and 2-(3 - mercaptobenzoyl) - HPI can also be prepared analogously.

Example 26.

a) 1.15 g. sodium borohydride is added portionwise at 0°C. to 6.5 g. 2 - (4 - oxocyclohexyl - carbonyl) - HPI in 100 ml. ethanol. The reaction mixture is stirred for 12 hours at 20°C. and then poured on to ice to give 2 - (4 - hydroxycyclohexyl - carbonyl)-HPI as an isomeric mixture.

b) 24 ml. of a 0.5M solution of potassium tris - (*sec.* - butyl) - borohydride in tetrahydrofuran is added, under nitrogen at −70°C., to a solution of 3.25 g. 2 - (4 - oxocyclohexyl - carbonyl) - HPI in 35 ml. anhydrous tetrahydrofuran. After 3 hours, the reaction mixture is mixed with 35 ml. water, allowed to warm up to 20°C. and then worked up with chloroform. After purification on silica gel, using chloroform, *cis* - 2 - (4 - hydroxycyclohexyl - carbonyl) - HPI is obtained; m.p. 162—163°C.

Example 27.

6.5 g. 2 - (4 - oxocyclohexyl - carbonyl)-HPI in 100 ml. methanol are hydrogenated in the presence of 2 g. Raney nickel at 50°C. and 100 ats. up to saturation. The catalyst is filtered off and the solvent is evaporated to give 2 - (4 - hydroxycyclohexyl - carbonyl)-HPI as an isomeric mixture.

Example 28.

3.16 g. 2 - (4 - oxocyclohexyl - carbonyl)-HPI are hydrogenated for 10 hours in 100 ml. methanol, which has been saturated with ammonia at 10°C., in the presence of 1 g. Raney nickel and 100 ats. The catalyst is filtered off, the solvent is evaporated off and the residue is dissolved in ethanol. Hydrogen bromide in ethanol is added thereto and the product obtained is crystallised from ether to give *trans* - 2 - (4 - aminocyclohexylcarbonyl)-HPI hydrobromide; m.p. 285°C. Sodium hydroxide is added to the filtrate, followed by extraction with chloroform and evaporation to give *cis*-2-(4-aminocyclohexylcarbonyl)-HPI.

Example 29.

3.1 g. 2 - (4 - oximinocyclohexyl - carbonyl) - HPI (m.p. 194°C.; prepared from 2 - (4 - oxocyclohexyl - carbonyl) - HPI and hydroxylamine) are hydrogenated up to saturation in 100 ml. ethanol at room temperature and 5 ats. in the presence of 4 g. Raney nickel. Upon evaporation, 2 - (4 - aminocyclohexylcarbonyl)-HPI is obtained in the form of an isomeric mixture.

Example 30.

A solution of 5.5 g. 2 - isonicotinoyl - HPI and 6.3 g. 3 - chloroperbenzoic acid (50%) in methylene chloride is left to stand at 20°C. overnight. Ammonia is then passed up to saturation, followed by suction filtration and washing with methylene chloride. Evaporation of the filtrate gives 2-isonicotinoyl-HPI-1'-N-oxide, which melts at 250°C. after recrystallisation from ethanol.

Analogously, from 2 - nicotinoyl - HPI, there is obtained 2 -nicotinoyl - HPI - 1'-oxide; m.p. 178°C.

From the dialkylamino compounds mentioned in Example 1, there can be obtained analogously the corresponding N-oxides, for

example, 2 - (4 - dimethylaminobenzoyl)-HPI N-oxide.

Example 31.

3.2 g. 2 - (4 - dimethylaminobenzoyl)-HPI and 5 g. methyl iodide are heated overnight at 75°C. in 600 ml. acetonitrile. The solvent is evaporated off and the mixture obtained is purified on silica gel (eluent: chloroform/methanol) to give the methiodide of 2 - (4 - dimethylaminobenzoyl) - HPI which, after recrystallisation from ethanol, melts at 215—216°C.

Example 32.

2.1 g. 1 - aminocyclohexane - 1 - carboxylic acid are mixed with 6.3 g. trifluoroacetic anhydride and then 2 g. HPI and 2.3 g. triethylamine in 20 ml. methylene chloride are added at 0°C., whereafter the reaction mixture is warmed to 30°C. After an hour, the reaction mixture is poured into water, the organic phase is separated off, washed with aqueous sodium hydroxide solution and water, dried and evaporated to give 2 - (1 - aminocyclohexyl-1 - carbonyl) - HPI which, after recrystallisation from benzene, melts at 146°C.

The following compounds are obtained analogously:

2-methylaminoacetyl-HPI;
2-ethylaminoacetyl-HPI;
2-(2-methylamino-propionyl)-HPI;
2-(2-ethylamino-propionyl)-HPI;
2-(3-methylamino-propionyl)-HPI;
2-(3-ethylamino-propionyl)-HPI;
2-(2-methylamino-*n*-butyryl)-HPI;
2-(4-methylamino-*n*-butyryl)-HPI;
2-(4-ethylamino-*n*-butyryl)-HPI;
2-(2-methylamino-*n*-valeryl)-HPI;
2-(5-methylamino-*n*-valeryl)-HPI;
2 - (1 - methylaminocyclobutyl - carbonyl)-HPI;
2 - (2 - methylaminocyclobutyl - carbonyl)-HPI;
2 - (3 - methylaminocyclobutyl - carbonyl)-HPI;
2 - (1 - ethylaminocyclobutyl - carbonyl)-HPI;
2 - (2 - ethylaminocyclobutyl - carbonyl)-HPI;
2 - (3 - ethylaminocyclobutyl - carbonyl)-HPI;
2 - (1 - methylaminocyclopentyl - carbonyl)-HPI;
2 - (2 - methylaminocyclopentyl - carbonyl)-HPI;
2 - (3 - methylaminocyclopentyl - carbonyl)-HPI;
2 - (1 - ethylaminocyclopentyl - carbonyl)-HPI;
2 - (2 - ethylaminocyclopentyl - carbonyl)-HPI;
2 - (3 - ethylaminocyclopentyl - carbonyl)-HPI;
2 - (2,4 - diaminocyclohexyl - carbonyl) HPI;
2 - (3,4 - diaminocyclohexyl - carbonyl)-HPI;
2 - (3,5 - diaminocyclohexyl - carbonyl)-HPI;
2 - (1 - methylaminocyclohexyl - carbonyl)-HPI;
2 - (2 - methylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - methylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - methylaminocyclohexyl - carbonyl)-HPI;
2 - (1 - ethylaminocyclohexyl - carbonyl)-HPI;
2 - (2 - ethylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - ethylaminocyclohexyl - carbonyl)-HPI;
2 - (4 - ethylaminocyclohexyl - carbonyl)-HPI;
2 - [2,4 - bis - (methylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,4 - bis - (methylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,5 - bis - (methylamino) - cyclohexyl-carbonyl]-HPI;
2 - [2,4 - bis - (ethylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,4 - bis - (ethylamino) - cyclohexyl-carbonyl]-HPI;
2 - [3,5 - bis - (ethylamino) - cyclohexyl-carbonyl]-HPI;
2 - (4 - methylaminocycloheptyl - carbonyl)-HPI;
2 - (4 - ethylaminocycloheptyl - carbonyl)-HPI;
2-(2-methylaminobenzoyl)-HPI;
2-(3-methylaminobenzoyl)-HPI;
2 - (4 - methylaminobenzoyl) - HPI; m.p. 220°C.;
2-(2-ethylaminobenzoyl)-HPI;
2-(3-ethylaminobenzoyl)-HPI;
2-(4-ethylaminobenzoyl)-HPI;
2 - [3,4 - bis - (methylamino) - benzoyl-HPI;
2 - [3,5 - bis - (methylamino) - benzoyl]-HPI;
2 - [3,4 - bis - (ethylamino) - benzoyl]-HPI;
2 - [3,5 - bis - (ethylamino) - benzoyl]-HPI;
2-(3-aminopicolinoyl)-HPI;
2-(4-aminopicolinoyl)-HPI;
2-(5-aminopicolinoyl)-HPI;
2-(6-aminopicolinoyl)-HPI;
2-(3-methylaminopicolinoyl)-HPI;
2-(4-methylaminopicolinoyl)-HPI;
2-(5-methylaminopicolinoyl)-HPI;
2-(6-methylaminopicolinoyl)-HPI;
2-(2-aminonicotinoyl)-HPI;
2-(4-aminonicotinoyl)-HPI;
2-(5-aminonicotinoyl)-HPI;
2-(6-aminonicotinoyl)-HPI;

2-(2-methylaminonicotinoyl)-HPI;
2-(4-methylaminonicotinoyl)-HPI;
2-(5-methylaminonicotinoyl)-HPI;
2-(6-methylaminonicotinoyl)-HPI;
2-(benzimidazolyl-2-carbonyl)-HPI;
2-(pyrrolinyl-2-carbonyl)-HPI;
2-(pyrrolidinyl-2-carbonyl)-HPI;
2-(pyrrolidinyl-3-carbonyl)-HPI;
2 - (1,2,3,4 - tetrahydropyridyl - 1 - carbonyl)-HPI;
2 - (1,2,3,4 - tetrahydropyridyl - 2 - carbonyl)-HPI;
2-(piperidyl-1-carbonyl)-HPI;
2-(piperidyl-2-carbonyl)-EPI;
2-(piperidyl-3-carbonyl)-HPI;
2 - (piperidyl - 4 - carbonyl) - HPI monohydrate; m.p. 146—147°C.;
2 - (1,2,3,4 - tetrahydroquinolyl - 3 - carbonyl-HPI;
2 - (1,2,3,4 - tetrahydroquinolyl - 4 - carbonyl-HPI;
2 - (1,2,3,4 - tetrahydroisoquinolyl - 3 - carbonyl)-HPI;
2 - (1,2,3,4 - tetrahydroisoquinolyl - 1 - carbonyl)-HPI;
2 - (1,2,3,4 - tetrahydroisoquinolyl - 4 - carbonyl)-HPI.

If the organic phase is not washed with aqueous sodium hydroxide solution, then the corresponding trifluoroacetylamino compounds are also obtained, for example, 2-(1-trifluoroacetamidocyclohexyl-carbonyl)-HPI.

Example 33.

To a suspension of 4.2 g. of the "Leuchs Anhydride" of 4 - amino - tetrahydrothiopyran - 4 - carboxylic acid (1,3 - dioxo - 2-oxa-8-thiaspiro[4,5]decane; obtainable from this acid with phosgene) in 300 ml. chloroform, there are added 4.04 g. HPI and 1.5 g. acetic acid, whereafter the reaction mixture is boiled for 24 hours. The reaction mixture is then cooled and filtered and the filtrate washed with dilute aqueous sodium hydroxide solution and water and evaporated to give 2-(4-amino-tetrahydrothiopyran - 4 - carbonyl) - HPI which, after recrystallisation from ethyl acetate/ether/petroleum ether, melts at 157—158°C.

Example 34.

3.26 g. 2 - (4 - oxocyclohexyl - carbonyl)-HPI, 0.2 ml. water and 3.2 g. sulphur tetrafluoride in 50 ml. methylene chloride are shaken in an autoclave for 24 hours at 30°C. The reaction mixture is then poured into dilute sodium sulphate and evaporated to give 2-(4,4-difluorocyclohexylcarbonyl)-HPI.

Example 35.

3.4 g. 2 - (4 - mercaptobenzoyl) - HPI are heated on a water bath with 40 ml. nitric acid (d = 1.2). After subsidence of the initially vigorous reaction, the reaction mixture is evaporated to give 2-(4-sulphobenzoyl)-HPI.

In an analogous manner, by the oxidation of the corresponding mercapto compounds, there are obtained 2 - (2 - sulphobenzoyl)-HPI and 2-(3-sulphobenzoyl)-HPI.

Example 36.

Analogously to Example 17, 8 g. 2 - (4-acetoxybenzoyl)-HPI are saponified in the presence of 10% aqueous sodium hydroxide solution to give 2 - (4 - hydroxybenzoyl)-HPI; m.p. 243—245°C.

Analogously, by saponification of the appropriate acetates, there are obtained the following compounds:

2-(2-hydroxyacetyl)-HPI;
2-(2-hydroxycyclopropyl-carbonyl)-HPI;
2-(1-hydroxycyclobutyl-carbonyl)-HPI;
2-(2-hydroxycyclobutyl-carbonyl)-HPI;
2-(3-hydroxycyclobutyl-carbonyl)-HPI;
2-(1-hydroxycyclopentyl-carbonyl)-HPI;
2-(2-hydroxycyclopentyl-carbonyl)-HPI;
2-(3-hydroxycyclopentyl-carbonyl)-HPI;
2-(1-hydroxycyclohexyl-carbonyl)-HPI;
2-(2-hydroxycyclohexyl-carbonyl)-HPI;
2-(3-hydroxycyclohexyl-carbonyl)-HPI;
2-(4-hydroxycyclohexyl-carbonyl)-HPI;
(+) - 2 - (4 - hydroxycyclohexyl - carbonyl)-HPI;
(—) - 2 - (4 - hydroxycyclohexyl - carbonyl)-HPI;
2 - (2,4 - dihydroxycyclohexyl - carbonyl)-HPI;
2 - (3,4 - *cis* - dihydroxycyclohexyl - carbonyl)-HPI hydrate; m.p. 100—102°C.;
2 - (3,5 - dihydroxycyclohexyl - carbonyl)-HPI;
2 - (3,4,5 - trihydroxycyclohexyl - carbonyl)-HPI.

Example 37.

Analogously to Example 1, from HPI and 4 - (benzyloxycarbonylamino) - benzoyl chloride, there is prepared 2 - (4 - benzoyloxycarbonylaminobenzoyl)-HPI.

With the appropriately substituted acid halides, the following compounds are prepared analogously:

2 - (1 - methoxyacetamidocyclopentyl-carbonyl)-HPI;
2 - (1 - *tert.* - butoxycarbonylaminocyclopentyl-carbonyl)-HPI;
2 - (4 - benzyloxycarbonylaminocyclohexyl-carbonyl-HPI;
2 - [4 - (3,5 - dimethoxybenzyloxycarbonyl)-aminocyclohexylcarbonyl]-HPI;
2-(2-methoxyacetamidobenzoyl)-HPI;
2 - (2 - *tert.* - butoxycarbonylaminobenzoyl)-HPI;
2 - (2 - benzyloxycarbonylaminobenzoyl)-HPI:
2 - [2 - (3,5 - dimethoxybenzoyloxycarbonyl)-aminobenzoyl]-HPI;

2-(3-methoxyacetamidobenzoyl)-HPI;
2 - (3 - *tert.* - butoxycarbonylaminobenzoyl)-HPI;
2 - (3 - benzyloxycarbonylaminobenzoyl)-HPI;
2 - [3 - (3,5 - dimethoxybenzoyloxycarbonyl)-aminobenzoyl]-HPI;
2 - (4 - methoxyacetamidobenzoyl) - HPI; m.p. 172°C.;
2 - (4 - *tert.* - butoxycarbonylaminobenzoyl)-HPI;
2 - [4 - (3,5 - dimethoxybenzyloxycarbonyl)-aminobenzoyl]-HPI;
2 - (1 - *tert.* - butoxycarbonyl - piperidyl - 3-carbonyl)-HPI;
2 - (1 - benzyloxycarbonyl - piperidyl - 3-carbonyl)-HPI;
2 - [1 - (3,5 - dimethoxybenzyloxycarbonyl)-piperidyl-3-carbonyl]-HPI;
2 - (1 - benzyloxycarbonyl - piperidyl - 4-carbonyl)-HPI.

Example 38.

4.5 g. 2 - (1 - benzyloxycarbonyl-piperidyl - 3 - carbonyl) HPI are hydrogenated in 100 ml. 80% aqueous dioxan and 1 ml. acetic acid in the presence of 300 mg. palladium, whereafter the catalyst is filtered off, the filtrate is evaporated, the residue is taken up in chloroform, washed with an aqueous sodium carbonate solution and water and evaporated to give 2-(pyridyl-3-carbonyl)-HPI.

The following compounds are obtained analogously from the appropriate benzyloxycarbonylaminoacyl derivatives by hydrogenolysis:

trans - 2 - (4 - aminocyclohexyl - carbonyl)-HPI hydrobromide; m.p. 284°C.;
2 - (2 - aminobenzoyl) - HPI hydrobromide; m.p. 279—280°C.;
2 - (3 - aminobenzoyl) - HPI; m.p. 161—162°C.;
2 - (4 - aminobenzoyl) - HPI; m.p. 212—213°C.;
2 - (piperidyl - 4 - carbonyl) - HPI monohydrate; m.p. 146—147°C.

Example 39.

A solution of 4.3 g. 2 - (1 - *tert.*-butyloxycarbonyl - piperidyl - 3 - carbonyl) - HPI in 80 ml. 98% formic acid is left to stand for 5 hours at 20°C. The reaction mixture is evaporated and the residue is taken up in chloroform, washed with an aqueous sodium carbonate sultion and water and evaporated to give 2 - (piperidyl - 3 - carbonyl) - HPI.

Example 40.

A solution of 5.1 g. 2 - [1 - (3,5 - dimethoxybenzyloxycarbonyl) - piperidyl - 3 - carbonyl] - HPI in 100 ml. 80% aqueous dioxan is irradiated for 2 hours with a high pressure mercury lamp. The reaction mixture is mixed with hydrochloric acid, washed with ether, rendered alkaline with aqueous sodium hydroxide solution, extracted with chloroform and the extract evaporated to give 2 - (piperidyl-3-carbonyl)-HPI.

Example 41.

6.4 g 2 - (4 - aminobenzoyl) - HPI, 2.7 g. salicylaldehyde and 100 mg. *p*-toluenesulphochloride in 150 ml. toluene are boiled for 12 hours, with removal of the water formed. The reaction mixture is evaporated and the residue is triturated with ether to give 2-(4-*o* - hydroxybenzylidene - amino - benzoyl)-HPI which, after recrystallisation from benzene/petroleum ether, melts at 196—197°C.

In an analogous manner but using benzaldehyde, there is obtained 2-(4-benzylideneamino-benzoyl)-HPI.

Example 42.

3 g. 2-(4-benzylideneamino-benzoyl)-HPI in 50 ml. methanol are hydrogenated in the presence of 1 g. platinum for 3 hours at 20°C. and atmospheric pressure. After filtering off of the catalyst and evaporation, there is obtained 2 - (4 - benzylamino - benzoyl) - HPI; m.p. 204—205°C.

The following compounds are obtained analogously by hydrogenation of the appropriate Schriff bases:

2 - (3 - benzylamino - cycloypentyl - carbonyl)-HPI;
2 - (4 - benzylamino - cyclohexyl - carbonyl)-HPI;
2-(3-benzylamino-benzoyl)-HPI;
2 - [3 - (2 - hydroxybenzyl) - aminocyclopentyl-carbonyl]-HPI;
2 - [4 - (2 - hydroxybenzyl) - aminocyclohexyl-carbonyl]-HPI;
2 - [3 - (2 - hydroxybenzyl) - aminobenzoyl]-HPI;
2 - [4 - (2 - hydroxybenzyl) - aminobenzoyl]-HPI; m.p. 201—202°C.;
2 - [3 - (2 - hydroxy - 3 - methoxybenzyl)-aminocyclopentylcarbonyl]-HPI;
2 - [4 - (2 - hydroxy - 3 - methoxybenzyl)-aminocyclohexyl-carbonyl]-HPI;
2 - [3 - (2 - hydroxy - 3 - methoxybenzyl)-aminobenzoyl]-HPI;
2 - [4 - (2 - hydroxy - 3 - methoxybenzyl)-aminobenzoyl]-HPI;
2 - (3 - carboxymethylaminocyclopentyl-carbonyl)-HPI;
2 - (4 - carboxymethylaminocyclohexyl-carbonyl)-HPI;
2 - (3 - carboxymethylaminobenzoyl) - HPI;
2 - (4 - carboxymethylaminobenzoyl) - HPI.

Instead of with platinum, the hydrogenation can also be carried out with Raney nickel. Dioxan is used as solvent and the reaction is carried out at 45°C. and 1—5 atmospheres.

Example 43.

Analogously to Example 38, 2 - (4 - benzylideneaminobenzoyl)-HPI is hydrogenated in the presence of palladium to give 2 - (4-aminobenzoyl) - HPI; m.p. 212—213°C.

Example 44.

A diazonium solution prepared from 3.21 g. 2 - (4 - aminobenzoyl) - HPI, 5 ml. 6N hydrochloric acid, 0.7 g. sodium nitrite and 4 ml. water is allowed to flow into a solution of 1.38 g. salicylic acid in 15 ml. 2N aqueous sodium hydroxide solution at 5—10°C., care being taken that the solution remains alkaline. After half an hour, the product obtained is precipitated out with hydrochloric acid, filtered off, washed with water and a little ethanol and dried to give 2 -[4 - (3 - carboxy-4 - hydroxyphenylazo) - benzoyl] - HPI in the form of an orange-yellow powder; m.p. 241—244°C.

In an analogous manner, using anisole and dimethylaniline, there are obtained the following compounds:

2 - [4 - (4 - methoxyphenylazo) - benzoyl]-HPI; and
2 - [4 - (4 - dimethylaminophenylazo)-benzoyl]-HPI.

Example 45.

300 ml. of a 3.7 N solution of sodium bisulphate are heated for half an hour at 90°C. with 49 g. cinnamyl aldehyde. 111.7 g. 2-(4-aminobenzoyl)-HPI in 1 litre dioxan are added thereto and the reaction mixture is heated for 12 hours at 90°C. After cooling, the reaction mixture is extracted with chloroform; the aqueous phase is concentrated and the desired product is precipitated out by the addition of ethanol. There is obtained the disodium salt of 2 - [4 - (1,3 - disulpho - 3-phenylpropylamino) - benzoyl] - HPI; m.p. 221—222°C. (decomposition).

Example 46.

From 2 - (4 - aminobenzoyl) - HPI and allyl iodide, there is prepared, analogously to Example 24, 2 - (4 - allylaminobenzoyl)-HPI.

The following compounds are also obtained analogously:

2 - (3 - allylaminocyclopentyl - carbonyl)-HPI;
2 - (4 - allylaminocyclohexyl - carbonyl)-HPI;
2 - (3 - allylaminobenzoyl) - HPI.

Example 47.

Analogously to Example 5, from the appropriate amino compounds and succinic, maleic or phthalic anhydride, there are obtained the following compounds:

2-(4-succinylamino-benzoyl)-HPI;
2-(4-maleinoylamino-benzoyl)-HPI;
2-(4-phthaloylamino-benzoyl)-HPI;
2 - (1 - succinyl - piperidinyl - 4 - carbonyl)-HPI;
2 - (1 - phthaloyl - piperidyl - 4 - carbonyl)-HPI.

Example 48.

4.8 g. 2 - (3 - cyclohexyl - 1 - carbonyl)-HPI and 4 g. osmium tetroxide in 60 ml. pyridine are stirred overnight at 20°C. A solution of 7 g. sodium bisulphite in 100 ml. water and 85 ml. pyridine is then added thereto and the mixture is stirred for 30 minutes and extracted with methylene chloride. After drying and evaporating, there is obtained 2-(3,4-*cis* - dihydroxycyclohexyl - 1 - carbonyl)-HPI hydrate; m.p. 100—102°C.

Example 49.

3.1 g. 2 - (3 - cyclohexenyl - 1 - carbonyl)-HPI are hydrogenated in 100 ml. methanol in the presence of 300 mg. platinum oxide at 20°C. and atmospheric pressure until the reaction stops. The reaction mixture is filtered and the filtrate is evaporated to give 2 - cyclohexylcarbonyl-HPI; m.p. 136—138°C.

Example 50.

A solution of 3.3 g. 2 - (tetrahydrothiopyran - 4 - carbonyl) - HPI and 1.05 ml. 30% aqueous hydrogen peroxide in 20 ml. acetic acid is left to stand overnight at 20°C. and then evaporated and worked up with chloroform and water to give 2 - (tetrahydrothiopyran - 4 - carbonyl) - HPI - S - oxide in the form of an isomeric mixture; m.p. 175—180°C.

Example 51.

3.3 g. 2 -(tetrahydrothiopyran - 4 - carbonyl)-HPI and 2.5 ml. 30% aqueous hydrogen peroxide in 25 ml. acetic acid is heated to 60°C. for 2 hours and then evaporated and worked up with chloroform and water to give 2 - (tetrahydrothiopyran - 4 - carbonyl)-HPI - S,S - dioxide which, after recrystallisation from ethanol, melts at 253—255°C.

Example 52.

35 ml. of a 0.5 M solution of potassium tri-*sec.*-butyl borohydride in tetrahydrofuran is slowly added, under nitrogen and at −70°C., to a solution of 4.9 g. 2 - (4 - oxocyclohexylcarbonyl) - HPI in 50 ml. anhydrous tetrahydrofuran. After 3 hours, the reaction mixture is mixed with 50 ml. water, allowed to warm up to ambient temperature and then acidified with hydrochloric acid and extracted with chloroform. The chloroform extract is purified chromatographically (silica gel/chloroform). There is obtained pure *cis* - 2 - (4 - hydroxycyclohexyl - carbonyl) - HPI which, after recrystallisation from isopropanol/diethyl ether, melts at 162—163°C.

The active materials of general formula (I) can be worked up by methods known from and described in the literature, to give pharmaceutical compositions, as is shown by the following Examples.

Example 53.

Tablets for combating cestodes (adults).

a) Tablets containing 500 mg. 2-cyclohexylcarbonyl-HPI as active material are prepared from a powder mixture consisting of 5 kg. 2 - cyclohexylcarbonyl - HPI, 3 kg. lactose, 1.8 kg. maize starch and 0.2 kg. magnesium stearate.

b) The mixture described in Example 53 a) can also be used for making tablets containing 50 mg., 250 mg. and 1000 mg. 2-cyclohexylcarbonyl-HPI.

The tablets containing 250 mg. and 500 mg. 2 - cyclohexylcarbonyl - HPI as active material are preferably used in human medicine. However, all the tablets can also be used in veterinary medicine.

Example 54.

Tablets for combating cestode hydatids and schistosomes.

a) *Effervescent tablets.*

Each tablet contains:

2-cyclohexylcarbonyl-HPI	1000 mg.
citric acid	800 mg.
sodium carbonate	900 mg.
saccharin	5 mg.
saccharose	ad 4000 mg.

b) *Sugar chewable tablets.*

Each tablet contains:

2-cyclohexylcarbonyl-HPI	2000 mg.
cellulose	80 mg.
sodium carboxymethyl-cellulose	40 mg.
colouring and aroma	as desired
saccharose	ad 4000 mg.

Example 55.

Dragees for combating cestodes in human medicine.

Each dragee core contains:

2-cyclohexylcarbonyl-HPI	250 mg.
lactose	150 mg.
maize starch	90 mg.
magnesium stearate	10 mg.

The dragee coating consists of talc, saccharose, titanium dioxide, calcium carbonate, polyvinylpyrrolidone, methyl cellulose, glycerol, magnesium oxide and lacquer.

This formulation can also be used for dragees which contain 500 mg. 2-cyclohexylcarbonyl-HPI as active material.

Example 56.

Syrup for combating cestodes in human medicine.

The syrup is produced by making a suspension consisting of:

2-cyclohexylcarbonyl-HPI	3.5 kg.
distilled water	2 litres
buffer	0.1 litres
glycerol	3 kg.
sorbitol	3 kg.
saccharose	53 kg.
a mixture of 60% methyl *p*-hydroxybenzoate and 40% propyl *p*-hydroxybenzoate	0.1 kg.
ethanol	12 litres.

This mixture is mixed with colouring and aroma materials and made up to 100 litres with distilled water.

Example 57.

Capsules for combating cestodes and schistosomes in human and veterinary medicine.

Capsules of appropriate size are filled with a mixture of:

2-cyclohexylcarbonyl-HPI	5000 mg.
talc	250 mg.
magnesium stearate	150 mg.

In the same way, capsules are produced containing 1000 mg. and 10,000 mg. of 2-cyclohexylcarbonyl-HPI.

Example 58.

Injection liquid for human and veterinary medicine.

For subcutaneous administration in oily or aqueous suspension, 15 mg. ampoules are filled with a solution of 500 mg. 2-cyclohexylcarbonyl-HPI in 6 ml. water and 4 ml. propylene glycol, with the addition of a solubilising agent. The ampoules are heat sterilised and a preservation agent added thereto.

Similarly, ampoules are produced containing 100 mg. 2 - cyclohexylcarbonyl - HPI (for small animals) and 1000 mg. 2 - cyclohexylcarbonyl-HPI (for large animals).

Example 59.

Pellets.

A powder mixture is prepared from equal parts by weight of 2 - cyclohexylcarbonyl-HPI and lactose and then, together with sodium carboxymethylcellulose, worked up in known manner to give a uniform granulate with an average particle size of 1.5 mm.

Example 60.

Veterinary medicinal pre-mixture suitable for admixture with an animal feed as carrier to give a medicated feed.

a) 25% pre-mixture (preferably for large animals).

25 kg. 2 - cyclohexylcarbonyl - HPI are mixed with 75 kg. fine bran (obtained in the milling of wheat) and/or lactose.

b) 5% pre-mixture (preferably for small animals).

5 kg. 2 - cyclohexylcarbonyl - HPI are worked up in a manner analogous to Example 60 a).

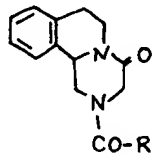
c) Example of the use of a pre-mixture produced according to Example 60 a) for combating types of *Moniezia* in bovine intestines.

In order to obtain a suitable medicated feed, 1 kg. of the pre-mixture produced according to Example 60 a) is mixed with 9 kg. of a conventional feed concentrate. 400 g. of this medicated feed, containing 10,000 mg. 2-cyclohexylcarbonyl-HPI, are administered for combating *Moniezia* infestation of adult cattle.

In a manner analogous to that described in Examples 53 to 60, instead of 2-cyclohexylcarbonyl-HPI, there can be used other active materials of general formula (I) and/or physiologically compatible salts thereof for the production of pharmaceutical compositions.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein COR is an acyl radical containing up to 26 carbon atoms derived from an unsubstituted or substituted aliphatic, cycloaliphatic, cycloalkyl aliphatic, arylaliphatic or heterocyclic carboxylic acid or a substituted aromatic carboxylic acid by removal of the hydroxyl group from the carboxylic radical; the physiologically compatible salts, the quaternary ammonium salts and the optical antipodes thereof.

2. 2 - (4 - Nitrobenzoyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

3. 2 - Acetyl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

4. 2 - Isobutyryl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

5. 2 - Trimethylacetyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

6. 2 - (3,3 - Dimethyl - *n* - butyryl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

7. 2 - (2,2 - Dimethylvaleryl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

8. 2 - (2 - *n* - Butylhexanoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

9. 2 - Hexadecanoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

10. 2 - Dichloroacetyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

11. 2 - Trichloroacetyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

12. 2 - Tris - (chloromethyl) - acetyl - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

13. 2 - (2 - Methoxyacetyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

14. 2 - (2 - Phenylacetyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

15. 2 -(2 - Acetoxy - 2 - phenylacetyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1a]isoquinoline.

16. 2 - (4 - Chlorophenoxyacetyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

17. 2 - (Thienyl - 2 - mercaptoacetyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1a]isoquinoline.

18. 2 - Cinnamoyl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1a]isoquinoline.

19. 2 - Phenylpropiolyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

20. 2 - Phenoxycarbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

21. 2 - Ethoxalyl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

22. 2 - Cyclopropyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

23. 2 - Cyclobutyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

24. 2 - Cyclopentyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

25. 2 - Cyclohexyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

26. 2 - (3 - Cyclohexenyl - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

27. 2 - (4 - Ketocyclohexyl - carbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

28. 2 - Cycloheptyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

29. 2 - Cyclooctyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1a]isoquinoline.

30. 2 - Cycloundecyl - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

31. 2 - (Adamantyl - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

32. 2 - (3 - Methylbenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

33. 2 - (4 - Methylbenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

34. 2 - (4 - *tert.* - Butylbenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
35. 2 - (2 - Fluorobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
36. 2 - (3 - Fluorobenzoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
37. 2 - (4 - Fluorobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
38. 2 - (3 - Chlorobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
39. 2 - (4 - Chlorobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
40. 2 - (3,5 - Dichlorobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
41. 2 - (2,3,4,5,6 - Pentafluorobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
42. 2 - (3 - Hydroxybenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
43. 2 - (4 - Hydroxybenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
44. 2 - (3,5 - Dihydroxybenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
45. 2 - (4 - Methoxybenzoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
46. 2 - (4 - Dimethylaminobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
47. 2 - (3 - Formamidobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
48. 2 - (4 - Formamidobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
49. 2 - (4 - Acetamidobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
50. 2 - (4 - Methylthiobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
51. 2 - (2 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
52. 2 - (3 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
53. 2 - (3,4 - Dinitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
54. 2 - (3,5 - Dinitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
55. 2 - (3 - Trifluoromethylbenzyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
56. 2 - (4 - Cyanobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
57. 2 - (4 - Methoxycarbonylbenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
58. 2 - (2 - Chloro - 4 - nitrobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
59. 2 - (4 - Chloro - 3 - nitrobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
60. 2 - (2 - Hydroxy - 5 - chlorobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
61. 2 - Napthyl - 1 - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
62. 2 - Naphthyl - 2 - carbonyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
63. 2 - (Pyrryl - 2 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
64. 2 - (Thienyl - 2 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
65. 2 - (Thienyl - 3 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
66. 2 - (5 - Nitrothienyl - 2 - carbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
67. 2 - (5 - Methyl - thienyl - 2 - carbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
68. 2 - (Furyl - 2 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
69. 2 - (5 - Bromofuryl - 2 - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
70. 2 - (5 - Nitrofuryl - 2 - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
71. 2 - (Indolyl - 5 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.
72. 2 - (5 - Methyl - pyrazolyl - 3 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.
73. 2 - (Thiazolyl - 4 - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.
74. 2 - (2,4 - Dimethyl - thiazolyl - 5-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.
75. 2 - (5 - Methyl - isoxazolyl - 3 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.
76. 2 - Picolinoyl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.
77. 2 - Nicotinoyl - 4 - oxo - 1,2,3,6,7,11*b*-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

78. 2 - (4 - Chloronicotinoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

79. 2 - Isonicotinoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

80. 2 - (2,6 - Dichloroisonicotinoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

81. 2 - (Quinolyl - 2 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

82. 2 - (Isoquinolyl - 1 - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

83. 2 - (Pyrazinoyl - 2 - carbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

84. 2 - (4 - Methyl - piperazinyl - 1 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

85. 2 - (1 - Methyl - 1,2,5,6 - tetrahydropyridyl - 3 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

86. 2 - (1 - Formylpiperidyl - 4 - carbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

87. 2 - (Tetrahydropyranyl - 4 - carbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

88. 2 - (Chromon - 2 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

89. 2 - (Tetrahydrothiopyranyl - 4 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

90. 2 - (2,1,3 - Benzothiadiazolyl - 5-carbonyl) - 4 - oxo - 1,2,3,6,7,11b-hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

91. 2 - Formyl - 4 - oxo - 12,3,6,7,11*b*-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

92. 2 - (2 - *trans* - Carboxy - cyclohexyl-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

93. 2 - (2 - *cis* - Carboxy - cyclohexyl-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a]isoquinoline.

94. (+) - 2 - Cyclohexyl - carbonyl - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

95. (−) - 2 - Cyclohexyl - carbonyl - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

96. (+) - 2 - (4 - Methoxybenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

97. (−) - 2 - (4 - Methoxybenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

98. (+) - 2 - (4 - *tert.* - Butylbenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

99. (−) - 2 - (4 - *tert.* - Butylbenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

100. (+) - 2 - (2 - Fluorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

101. (−) - 2 - (2 - Fluorobenzoyl) - 4-xo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

102. (+) - 2 - (3 - Fluorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

103. (−) - 2 - (3 - Fluorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

104. (+) - 2 - (4 - Fluorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

105. (−) - 2 - (4 - Fluorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

106. (+) - 2 - (4 - Chlorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

107. (−) - 2 - (4 - Chlorobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

108. (+) - 2 - (4 - Methoxybenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

109. (−) - 2 - (4 - Methoxybenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

110. (+) - 2 - (4 - Formamidobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

111. (−) - 2 - (4 - Formamidobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

112. (+) - 2 - (3 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

113. (−) - 2 -(3 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

114. (+) - 2 - (4 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

115. (−) - 2 - (4 - Nitrobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

116. (+) - 2 - Nicotinoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

117. (−) - 2 - Nicotinoyl - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

118. 2 - (4 - Aminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

119. *cis* - 2 -(4 - Aminocyclohexyl - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

120. *trans* - 2 - (4 - Aminocyclohexyl-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

121. 2 - (2 - Aminobenzoyl) - 4 - oxo-

1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

122. 2 - (3 - Aminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

123. (+) - 2 - (3 - Aminobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

124. (−) - 2 - (3 - Aminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

125. (+) - 2 - (4 - Aminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

126. (−) - 2 - (4 - Aminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

127. 2 - (3,4 - Diaminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

128. 2 - (3,5 - Diaminobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

129. 2 - (2 - Chloro - 4 - aminobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

130. 2 - (3 - Amino - 4 - chlorobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

131. 2 - (4 - Amino - tetrahydrothiopyranyl-4 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino[2,1-a] isoquinoline.

132. 2 - [4 - (1 - Methylhydrazino)-benzoyl] - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

133. 2 - (4 - Carboxamidobenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

134. 2 - (4 - Carboxybenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

135. 2 - (4 - Acetoxybenzoyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

136. 2 - (4 - Methylaminobenzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

137. *cis* - 2 - (4 - Hydroxycyclohexyl-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

138. 2 - (4 - Aminocyclohexylcarbonyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

139. 2 - (1 - Aminocyclohexyl - 1 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

140. 2 - (Piperidyl - 4 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

141. 2 - (4,4 - Difluorocyclohexylcarbonyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

142. 2 - (3,4 - *cis* - Dihydroxycyclohexyl-carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

143. 2 - (4 - Methoxyacetamidobenzoyl)-4 - oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

144. 2 - (Piperidyl - 3 - carbonyl) - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

145. 2 - (4 - *o* - Hydroxybenzylideneamino-benzoyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

146. 2 - (4 - Benzylamino - benzoyl) - 4-oxo - 1,2,3,6,7,11*b* - hexahydro - 4H-pyrazino[2,1-a]isoquinoline.

147. 2 - [4 - (2 - Hydroxybenzyl) - amino-benzoyl] - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline.

148. 2 - [4 - (3 - Carboxy - 4 - hydroxy-phenylazo) - benzoyl] - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

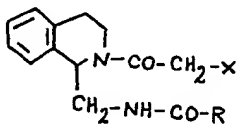
149. 2 - [4 - (1,3 - Disulpho - 3 - phenyl-propylamino) - benzoyl] - 4 - oxo-1,2,3,6,7,11*b* - hexahydro - 4H - pyrazino-[2,1-a]isoquinoline.

150. 2 - (Tetrahydrothiopyran - 4 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H-pyrazino[2,1-a]isoquinoline S-oxide.

151. 2 - (Tetrahydrothiopyran - 4 - carbonyl) - 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H - pyrazino[2,1-a]isoquinoline S,S-dioxide.

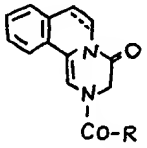
152. Process for the preparation of compounds of the general formula given in claim 1, wherein 4 - oxo - 1,2,3,6,7,11*b* - hexahydro-4H - pyrazino[2,1-a]isoquinoline is reacted with an acid of the general formula R.COOH, in which R has the same meaning as above, or with a functional derivative thereof.

153. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



in which R has the same meaning as in claim 1 and X is a fluorine, chlorine, bromine or iodine atom or a methylsulphonyloxy or arylsulphonyloxy radical containing 6 to 10 carbon atoms, is cyclised in the presence of a cyclising agent under conditions splitting off HX.

154. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula::—



in which R has the same meaning as in claim

1 and the broken line indicates the optional presence of a double bond in the 6,7-position of the ring system, is reacted with a reducing agent.

155. Process according to any of claims 152 to 154, wherein the substituent R in the product obtained is replaced by a different substituent R in a manner known from and described in the literature.

156. Process according to any of claims 152 to 155, wherein optically-active starting materials are used to give optically-active products.

157. Process according to any of claims 152 to 155, wherein racemic starting materials are used and the product obtained is resolved into its optically-active isomers.

158. Process according to any of claims 152 to 157, wherein, when the product obtained is a base, it is converted into an acid-addition salt or into a quaternary ammonium salt.

159. Process according to any of claims 152—157, wherein, when the product obtained is an acid-addition salt, the base is liberated therefrom.

160. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

161. Compounds according to claim 1, whenever prepared by the process according to any of claims 152 to 160.

162. Anthelmintic, comprising an effective dose of at least one compound according to claim 1, in admixture with a solid, liquid or semi-liquid pharmaceutical diluent or carrier or in admixture with an animal feed or feed concentrate.

163. Anthelmintic according to claim 162 for oral administration, wherein at least one sweetening and/or flavouring agent is additionally present.

164. Anthelmintic according to claim 162 or 163, wherein the liquid or semi-liquid diluent or carrier contains at least one emulsifying and/or dispersing agent.

165. Anthelmintic according to any of claims 162 to 164, wherein the liquid diluent or carrier is water.

166. Anthelmintic according to claim 165, wherein the water contains an auxiliary solvent.

167. Anthelmintic, comprising an effective dose of at least one compound according to claim 1 in a capsule.

168. Anthelmintic according to claim 167, wherein the capsule additionally contains a solid, liquid or semi-liquid pharmaceutical diluent or carrier.

169. Anthelmintic according to any of claims 162 to 168, wherein at least one additional active material is also present.

170. Anthelmintic according to any of claims 162 to 169, substantially as hereinbefore described and exemplified.

171. A method of treating helminthiasis in veterinary medicine, which comprises administering an effective dose of at least one compound according to claim 1.

172. A method of treating helminthiasis in veterinary medicine, which comprises administering an anthelmintic according to any of claims 162 to 171.

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